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TABLE OF CONTENTS

1 INTRODUCTION AND OBJECTIVES OF ANALYSIS 10

1.1 INTRODUCTION 10

1.2 OBJECTIVES OF STATISTICAL ANALYSIS 10

1.2.1 PRIMARY OBJECTIVE OF STATISTICAL ANALYSIS 10

1.2.2 KEY SECONDARY OBJECTIVES OF STATISTICAL ANALYSIS 10

1.2.3 OTHER SECONDARY 11

1.2.4 EXPLORATORY 11

2 STUDY DESIGN 13

2.1 SYNOPSIS OF STUDY DESIGN 13

2.2 RANDOMIZATION METHODOLOGY 13

2.3 STOPPING RULES AND BLINDING 13

2.3.1 STOPPING RULES 13

2.3.2 BLINDING 14

2.4 STUDY PROCEDURES 14

2.5 EFFICACY, PHARMACOKINETIC, AND SAFETY VARIABLES 28

2.5.1 EFFICACY VARIABLES 28

2.5.2 PHARMACOKINETIC VARIABLES 29

2.5.3 SAFETY VARIABLES 29

2.5.4 EXPLORATORY VARIABLES 30

3 SUBJECT POPULATIONS 31

3.1 POPULATION DEFINITIONS 31

3.2 PROTOCOL DEVIATIONS 33

4 STATISTICAL METHODS 34

4.1 SAMPLE SIZE JUSTIFICATION 34

4.2 GENERAL STATISTICAL METHODS AND DATA HANDLING 34

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4.2.1 GENERAL METHODS ... 34
4.2.2 COMPUTING ENVIRONMENT ... 35
4.2.3 REFERENCE START DATE, BASELINE DEFINITIONS, AND STUDY DAY ... 35
4.2.4 METHODS OF POOLING DATA ... 35
4.2.5 ADJUSTMENTS FOR COVARIATES ... 35
4.2.6 MULTIPLE COMPARISONS/MULTIPLICITY ... 35
4.2.7 SUBPOPULATIONS ... 37
4.2.8 WITHDRAWALS, DROPOUTS, LOST TO FOLLOW-UP ... 38
4.2.9 MISSING, UNUSED, AND SPURIOUS DATA ... 38
4.2.10 VISIT WINDOWS ... 38
4.3 INTERIM ANALYSES ... 38
4.4 SUBJECT DISPOSITION ... 39
4.5 DEMOGRAPHIC AND BASELINE CHARACTERISTICS ... 39
4.6 MEDICAL HISTORY, DISEASE HISTORY AND PRIOR THERAPIES ... 40
4.7 EFFICACY EVALUATION ... 42
4.7.1 PRIMARY EFFICACY ENDPOINTS ... 42
4.7.2 KEY SECONDARY EFFICACY ENDPOINTS ... 45
4.7.3 OTHER SECONDARY EFFICACY ENDPOINTS ... 47
4.7.4 SUBGROUP ANALYSES ... 50
4.8 PATIENT REPORTED OUTCOMES (PROS) ... 51
4.8.1 EQ-5D-5L ... 51
4.8.2 EORTC-QLQ-C30 ... 51
4.8.3 PRO-CTCAE ... 54
4.8.4 SENSITIVITY ANALYSES ... 54
4.8.5 EXPLORATORY ANALYSES ... 54
4.9 PHARMACOKINETIC EVALUATIONS ... 55
4.10 EXPLORATORY ANALYSIS ... 55
4.11 INDEPENDENT DATA MONITORING COMMITTEE ... 55

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4.12 SAFETY ANALYSES 55

4.12.1 TREATMENT EXPOSURE 55

4.12.2 ADVERSE EVENTS 57

4.12.3 LABORATORY DATA 59

4.12.4 VITAL SIGNS 60

4.12.5 ELECTROCARDIOGRAM 61

4.12.6 PRIOR AND CONCOMITANT MEDICATIONS 62

4.12.7 ECOG PERFORMANCE STATUS 62

5 COVID-19 IMPACT 63

5.1 COVID-19 OVERALL IMPACT ON SCHEDULED ASSESSMENTS 63

5.2 BY-SUBJECT COVID-19 LISTINGS 63

5.3 BY-SITE AND BY-COUNTRY COVID-19 IMPACT 63

6 CHANGES TO PLANNED ANALYSES 64

7 REFERENCES 65

8 CLINICAL STUDY REPORT APPENDICES 66

8.1 MISSING DATE IMPUTATION CONVENTION 66

8.1.1 ADVERSE EVENT (AE) START (ONSET) DATE AND STOP DATE IMPUTATION 66

8.1.2 CONCOMITANT MEDICATION (CM) START DATE AND STOP DATE IMPUTATION 67

8.1.3 OTHER DATE IMPUTATIONS 67

8.2 CRITERIA FOR ABNORMAL VALUES FOR VITAL SIGNS 67

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Protocol RAD1901-308

ELACESTRANT MONOTHERAPY VS. STANDARD OF CARE FOR THE TREATMENT OF PATIENTS WITH ER+/HER2- ADVANCED BREAST CANCER FOLLOWING CDK4/6 INHIBITOR THERAPY: A PHASE 3 RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED, MULTICENTER TRIAL

(EMERALD)

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Sponsor:	Radius Pharmaceuticals, Inc. 22 Boston Wharf Road, 7th Floor Boston, MA 02201 Tel: 617-551-4000
Sponsor Representative:	Maureen Conlan, MD Senior Vice President, Head of Oncology
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SIGNATURE PAGE

Protocol Title:	ELACESTRANT MONOTHERAPY VS. STANDARD OF CARE FOR THE TREATMENT OF PATIENTS WITH ER+/HER2- ADVANCED BREAST CANCER FOLLOWING CDK4/6 INHIBITOR THERAPY: A PHASE 3 RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED, MULTICENTER TRIAL (EMERALD)
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Document Date/Version:	25 March 2020/6.0
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Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, and all applicable regulatory guidance's and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report (CSR).

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Sponsor Signatory:

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Boston, MA 02201

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Senior Vice President, Head of Oncology

Signature:_____

Date:_____

LIST OF IN-TEXT TABLES

Table **Page**

Table 1 Schedule of Assessments 15
Table 2 Rules for Deriving Date of Progression or Censor for PFS 43
Table 3 Best Overall Responses when Confirmation of CR and PR Required 48
Table 4 EORTC QLQ-30 Scales and Items 52
Table 5 Criteria for Abnormal Vital Sign Values 67

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ABBREVIATIONS

Abbreviation	**Definition**
AE	Adverse event
AI	Aromatase inhibitor
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomic therapeutic class
BOR	Best overall response
CBE	Clinical benefit evaluable
CBR	Clinical benefit rate
CI	Confidence interval
CM	Concomitant medication
CR	Complete response
CRF	Case report form
CRO	Clinical Research Organization
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for AEs
ctDNA	Circulating tumor DNA
CV	Coefficient of variation
DCO	Data cut-off
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of treatment
EQ-5D-5L	EuroQoL 5 dimension, 5-level health state utility index
ER	Estrogen receptor
ER+	Estrogen receptor positive
ESMO	European society for medical oncology
ESR1	Estrogen receptor gene 1

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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)
EU	Europe
HER2-	Human epidermal growth factor receptor 2 negative
HR	Hazard ratio
HRQOL	Health-Related Quality of Life
IDMC	Independent data monitoring committee
IHC	Immunohistochemistry
IRC	Imaging review committee
IRT	Interactive randomization technology
ITT	Intent-to-treat
KM	Kaplan Meier
LFTs	Liver function tests
mBC	Advanced or metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
NA	North America
NCI	National Cancer Institute
NE	Not evaluable
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PIPS	Predicted interval plots
PK	Pharmacokinetic(s)
PP	Per-Protocol Population
PR	Partial response
PRO	Patient-reported outcome
PRO-CTCAE	Patient-reported outcome version of the Common Terminology Criteria for Adverse Events
PT	Preferred term

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Abbreviation	**Definition**
Q1	First quartile
Q3	Third quartile
QD	Once daily
QLQ-C30	30-item core quality-of-life questionnaire
RE	Response Evaluable
RECIST	Response Evaluation Criteria in Solid Tumors
RMST	Restricted Mean Survival Time
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SOC	Standard of Care
TEAE	Treatment-emergent adverse event
TTC	Time to chemotherapy
ULN	Upper limit of normal

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1 INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1 Introduction

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 standard of care (SOC) options of fulvestrant or an aromatase inhibitor (AI) in post-menopausal women and men with estrogen receptor (ER)-positive (+)/human epidermal growth factor receptor 2 (HER2)-negative (-) advanced or metastatic breast cancer (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.

1.2 Objectives of Statistical Analysis

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of study data in order to answer the study objective(s). Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

This SAP will also outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

1.2.1 Primary Objective of Statistical Analysis

- To compare progression-free survival (PFS) between elacestrant and SOC options of either fulvestrant or an AI based on a blinded Imaging Review Committee (IRC) assessment in post-menopausal women and men with ER+/HER2- mBC, either in subjects with estrogen receptor 1 (ESR1) mutation (ESR1-mut subjects) or in all subjects which includes subjects without detectable ESR1 mutation (ESR1-mut-nd).

1.2.2 Key Secondary Objectives of Statistical Analysis

- 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)

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1.2.3 Other Secondary

The following secondary objectives will be assessed in 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 in 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 in 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

1.2.4 Exploratory

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

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- To evaluate alterations in circulating tumor DNA (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 tissue, and to explore the relationship between these findings and clinical response

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2 STUDY DESIGN

2.1 Synopsis of Study Design

This is an international, multicenter, randomized, open-label, active-controlled, event-driven, Phase 3 study to compare 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 advanced or metastatic disease, which must have included CDK4/6 inhibitor therapy in combination with fulvestrant or an AI.

2.2 Randomization Methodology

The Investigators will randomize eligible subjects by Interactive Randomization Technology (IRT) as described in the IRT User Guide. Eligible subjects will be enrolled into the study and randomized in a 1:1 ratio to receive elacestrant 400 mg tablet once daily (QD) or SOC of either fulvestrant or an AI, stratified by

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

2.3 Stopping Rules and Blinding

2.3.1 Stopping Rules

An independent data monitoring committee (IDMC) external to both the Sponsor and 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. IDMC responsibilities and review schedules are outlined in an IDMC charter.

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)

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2.3.2 Blinding

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. The process of managing access to treatment information is documented in a blind management plan version final 3.0 dated 01FEB2021.

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

Unblinded 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.

2.4 Study Procedures

The schedule of assessments, as outlined in the study protocol, is provided in Table 1.

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Table 1 Schedule of Assessments

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						

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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 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						

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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						

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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)**
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]

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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]		

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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)**
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]	◄----------►						

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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.

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c. A Cycle is 28 days.

d. All assessments are to be performed pre-dose on scheduled visit days unless otherwise indicated. Procedures maybe 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 drug 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 of the protocol).

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 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.

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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 of the protocol.

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.

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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 of the protocol. 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 of the protocol. 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.

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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 of the protocol.

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 of the protocol.

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)

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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 drug 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.

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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 drug, the Investigator may report any SAE that he/she believes is related to study drug.

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.

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2.5 Efficacy, Pharmacokinetic, and Safety Variables

2.5.1 Efficacy Variables

2.5.1.1 Primary Efficacy Variables

The primary endpoints of this study are as follows:

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

where IRC-assessed PFS is defined as the time from randomization until the date of objective disease progression per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1; Appendix 1 of the protocol) as assessed by the blinded IRC, or death from any cause.

2.5.1.2 Key Secondary Efficacy Variables

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

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

2.5.1.3 Other Secondary Efficacy Variables

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-nd):

- Local Investigator-assessed PFS, defined as the 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 confirmed complete response (CR) or partial response (PR), based on blinded IRC assessment. To achieve a confirmed CR or PR, the confirmation scan must be repeated at least 4 weeks after the first documented response.
- IRC-assessed DoR defined as the duration of time from the date when criteria are met for CR or PR (whichever is first recorded) that is subsequently confirmed as assessed by IRC, per RECIST v1.1, until the first date of documented recurrent or progressive disease,

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objectively documented based on blinded IRC assessment, or death from any cause, whichever occurs first.

- IRC-assessed CBR, defined as the percentage of subjects who have achieved confirmed CR or PR any time during the study, or stable disease (SD) at ≥ 24 weeks from randomization per RECIST v1.1, based on blinded IRC assessment
- Local Investigator-assessed ORR, defined similarly as IRC-assessed ORR except using local Investigator assessment
- Local Investigator-assessed DoR, defined similarly as IRC-assessed DoR except using local Investigator assessment
- Local Investigator-assessed CBR, defined similarly as IRC-assessed CBR except using local Investigator assessment

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

- PRO endpoints assessed using the health-related quality of life (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 (EORTC QLQ-C30) and PRO Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE).

2.5.2 Pharmacokinetic Variables

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

- PK assessed by evaluation of elacestrant plasma concentrations at pre-dose (pretreatment) and 4 hours post-dose on Cycle 1 Day 1 (C1D1), pre-dose (C_{trough}) and 4 hours post-dose on Cycle 1 Day 15 (C1D15) and pre-dose (C_{trough}) on Cycle 2 Day 1 (C2D1)

2.5.3 Safety Variables

Safety and tolerability are assessed by treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (SAEs), dose modifications due to TEAEs, and clinical laboratory data (i.e., hematology, chemistry, and coagulation), electrocardiogram (ECG), ECOG performance status, and vital signs. Safety analyses will be performed for ESR1-mut subjects and all subjects (ESR1-mut and ESR1-mut-nd).

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2.5.4 Exploratory Variables

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

- Time to chemotherapy (TTC), defined as the time 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 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

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3 SUBJECT POPULATIONS

3.1 Population Definitions

The following populations will be defined and used for analysis:

- **Intent-to-Treat (ITT) Population**: The ITT population consists of all randomized subjects. This is the primary population for PFS and OS analysis. Subjects will be analyzed according to their randomized treatment assignment.
- **Per-Protocol (PP) Population**: The PP population consists of all randomized subjects who do not have any protocol deviations that could confound the interpretation of the primary analyses conducted on the ITT population. The PP population will be used to perform sensitivity analysis for the primary efficacy endpoint PFS if the primary endpoint is statistically significant. Subjects will be analyzed according to their randomized treatment assignment.

  Subjects with protocol deviations for any of the following criteria will be excluded from the PP population.

  Eligibility criteria:

  - Subject 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 (Protocol Inclusion Criteria 1)
  - Subject must have 1 of the following as defined by RECIST v1.1: (Protocol Inclusion Criteria 3)
    - Measurable disease
    - 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
  - Subject must have ER+ and HER2- tumor status confirmed per local laboratory testing (Protocol Inclusion Criteria 7)
  - Subject 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 for mBC (Protocol Inclusion criteria 8)
  - Subject 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 for mBC (Protocol Inclusion Criteria 9)

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- Subject must have received no more than 1 line of cytotoxic chemotherapy in the advanced/metastatic setting (Protocol Inclusion Criteria 10)
- Subject must have an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (Protocol Inclusion criteria 11)
- Subject must not have received prior treatment with elacestrant or investigational SERD or ER antagonist (Protocol Exclusion Criteria 1)
- Subject must not have received prior anti-cancer or investigational drug treatment within the protocol defined window period (Protocol Exclusion Criteria 2)
- Subject must not have difficulty in tolerating oral medications (Protocol Exclusion Criteria 12)
- Subject must not have taken a moderate or strong CYP3A4 inhibitor or inducer 14 days prior to study entry or during the study (Protocol Exclusion Criteria 13)

Other criteria:

- Subject did not provide main study informed consent
- Subject was randomized but did not receive any study drug
- Subject was treated with study drug they were not randomized to
- Subject received systemic anticancer therapy while on study drug
- Subject received radiation therapy to a target lesion

- **Safety Population**: The Safety population consists of all subjects who received at least 1 dose of study drug. All safety analyses will be performed using the Safety population. Subjects will be analyzed according to the treatments they actually received in Cycle 1.
- **Response Evaluable (RE) population**: The RE population includes all ITT subjects who had measurable disease (i.e., 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. IRC-assessed RE population will be defined using IRC assessment while Local Investigator-assessed RE population will be defined using Local Investigator assessment.

  IRC-assessed ORR and DoR will be analyzed using IRC-assessed RE population. Local Investigator-assessed ORR and DoR will be analyzed using Local Investigator-assessed RE population.
- **Clinical Benefit Evaluable (CBE) population**: The CBE population includes all ITT subjects who had measurable and/or evaluable disease (i.e., 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. IRC-assessed CBE population will be defined using IRC assessment while Local Investigator-assessed CBE population will be defined using Local Investigator assessment.

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IRC-assessed CBR will be analyzed using IRC-assessed CBE population. Local Investigator-assessed CBR will be analyzed using Local Investigator-assessed CBE population.

- **Pharmacokinetic (PK) Population**: The PK population consists of all subjects who received at least 1 dose of elacestrant and have plasma elacestrant concentration data for at least 1 scheduled time point. PK analyses will be performed using the PK population.
- **Biomarker Population**: The Biomarker population comprises all safety subjects for whom baseline and at least 1 post-baseline result are available for the biomarker of interest. The exploratory biomarker analysis will be performed using the Biomarker population.

3.2 Protocol Deviations

A major protocol deviation is defined as a deviation from basic requirements of the study protocol, including inclusion and exclusion criteria, concomitant medication restrictions, dosing (i.e., outside of ± 20% prescribed dose of study drug), or any protocol requirements that result in a significant added risk to the study participant or have an impact on the quality of the data collected or the outcome of the study. Major protocol deviations will be identified by Radius. The final list of Important Protocol Deviations that will exclude subjects from the PP populations will be imported to analysis data via an excel file. Major protocol deviations will be summarized by category, if applicable, and by treatment group in the ITT population. A by-subject data listing of all protocol deviations will also be provided.

At the discretion of the sponsor, major and important protocol deviations, as determined by a review of the data, may result in the exclusion of a subject's data from the PP population data set. The sponsor will be responsible for producing the final protocol deviation file (formatted as a Microsoft Excel file); this file will include a description of all protocol deviations, and clearly identify whether or not each deviation warrants exclusion from the PP population data set. This file will be finalized prior to database lock.

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4 STATISTICAL METHODS

4.1 Sample Size Justification

Note: This section describes the justification for the sample size used when the study was initiated and was based on PFS only. This amendment adds a truncated Hochberg procedure to allow testing of the key secondary endpoint of OS while maintaining the family-wise type I error rate at 5% (2-sided). At the time of this amendment, the study is fully enrolled (N=478) and the sample size will not be increased. Section 4.2.6 describes the testing procedures to be used for OS and the power associated with the OS analysis based on the number of OS events expected for the 478 subjects.

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 is selected to ensure that at least 1 of the 2 primary efficacy endpoints will pass the Hochberg procedure (Hochberg, 1988) to control the overall alpha level at 5.0% (see Section 4.2.6).

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 two treatment groups.

To prevent exceeding the target recruitment by more than 10% (i.e., 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 endpoint 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.

4.2 General Statistical Methods and Data Handling

4.2.1 General Methods

For continuous variables, descriptive statistics will include the number of subjects, mean, standard deviation, median, Q1, Q3, minimum, and maximum. For categorical variables, descriptive statistics will include the number of subjects, frequency counts and percentages. Time-to-event endpoints will be

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analyzed by the Kaplan-Meier method. When tabulating categorical data, "missing" will be included as a category and the number of subjects with missing data will be presented.

4.2.2 Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software (Version 9.4), unless otherwise noted. Medical History and adverse events will be coded using MedDRA version 23.0. Concomitant medications will be coded using World Health Organization (WHO) Drug version Sep2018.

4.2.3 Reference Start Date, Baseline Definitions, and Study Day

Baseline is defined as the last non-missing assessment prior to or on the first dose date. For subjects who are randomized but not dosed, baseline is defined as the last non-missing assessment prior to or on the date of randomization.

All data listings that contain an evaluation date will contain a relative study day. Study day is defined as the number of days relative to the reference start date. The reference start date is designated as Study Day 1. Study Day -1 is the day that precedes Study Day 1. There is no Day 0 in this study. Study Day will be calculated as follows:

- Before reference start date: Study Day = (Date of assessment – reference start date)
- On or After reference start date: Study Day = (Date of assessment – reference start date) + 1
- For efficacy assessments (tumor assessment, progression, death), the reference start date is date of randomization.
- For other assessments, the reference start date is the first dose date. For subjects who did not take any study drug, the reference start date is date of randomization.

4.2.4 Methods of Pooling Data

Data from all sites will be pooled for all analyses unless otherwise specified.

4.2.5 Adjustments for Covariates

The primary analysis will include the randomization strata collected from eCRF as the stratification factors. For the analyses of all subjects, these stratification factors include ESR1-mutation status (ESR1-mut vs ESR1-mut-nd), prior treatment with fulvestrant (yes vs no), and presence of visceral metastases (yes vs no). For the analyses of ESR1-mut subjects and ESR1-mut-nd subjects, the stratification factors include prior treatment with fulvestrant (yes vs no) and presence of visceral metastases (yes vs no).

4.2.6 Multiple Comparisons/Multiplicity

To ensure the family-wide error rate does not exceed 5%, multiplicity adjustments will account for the analyses of 2 primary endpoints, 2 key secondary OS endpoints, and the analyses of the key secondary OS endpoints at 2 time points. As described below, a truncated Hochberg procedure will be used to test the primary endpoints. The outcome of the analysis of the 2 PFS primary endpoints will determine

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the amount of alpha that will be passed to the analyses of OS. A Haybittle-Peto rule will be used to adjust the alpha for the analyses of OS at 2 time points.

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

OS is planned to be analyzed at the following 2 time points:

- At the time of the primary 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, and
- At the time of the final OS analysis (when approximately 50% of the subjects have died)

Although the sample size estimates were based on the conventional Hochberg procedure, a parallel gatekeeping strategy based on the truncated Hochberg procedure (Dmitrienko et al. 2011) will be used to control the family-wise type I error rate at 5% (2-sided) and to allow alpha to pass along from the analyses of the primary endpoint of PFS to the analyses of the key secondary endpoint of OS. The endpoint-specific alpha levels for the conventional Hochberg for this case are 0.05 and 0.05/2, and those for the equally weighted Bonferroni method are 0.05/2. The primary endpoint-specific alpha levels for the truncated Hochberg are constructed by combining the endpoint-specific alpha levels of the 2 methods with a truncation fraction. The analyses will use a truncation fraction of 0.9:

$\alpha_1 = 0.05*0.9 + 0.05/2*(1-0.9) = 0.0475$

$\alpha_2 = 0.05/2*0.9 + 0.05/2*(1-0.9) = 0.025$

To implement the truncated Hochberg procedure, the p-value for each of the 2 PFS primary endpoints will be derived without any adjustment. The larger p-value will be compared against α_1=0.0475. If the larger p-value is not less than 0.0475, the smaller p-value will be compared against α_2 = 0.025.

- If the larger p-value is <0.0475, statistical significance will be claimed for both PFS endpoints. An alpha of 0.05 will be passed along to OS. To control for the analyses of OS at the 2 time points, the alpha level of 0.05 will be distributed across the 2 time points. A 2-sided alpha level of 0.0001 will be allocated at the time of the primary PFS analysis and a 2-sided alpha level of 0.0499 will be allocated at the time of the final OS analysis. This alpha splitting is according to a Haybittle-Peto rule. At each time point, OS will be evaluated using the conventional Hochberg

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procedure and the allocated alpha to control for the multiple testing associated with the 2 populations.

- If the larger p-value is ≥0.0475 and the smaller p-value is <0.025, statistical significance will be claimed only for the endpoint associated with the smaller p-value. An alpha of 0.0025 will be passed along to OS only in the population in which PFS is significant. To control for the 2 different times the OS analysis will be conducted, the alpha level of 0.0025 will be distributed across the 2 time points. An alpha level of 0.0001 will be allocated at the time of the primary PFS analysis and an alpha level of 0.0024 will be allocated at the time of the final OS analysis. This adjustment is according to a Haybittle-Peto rule.
- If the larger p-value is ≥0.0475 and the smaller p-value is ≥0.025, no statistical significance will be claimed. In this case, no alpha will be passed along to OS. No claim regarding OS will be made.

OS will be evaluated at 2 time points: (1) at the time of the primary analysis of PFS and (2) when approximately 50% of all subjects (ESR1-mut and ESR1-mut-nd) have died. At the time of this amendment, the study is fully enrolled (N=478). The second analysis of OS will take place when approximately 239 subjects have died. At the time of the PFS analysis, it is expected that approximately 96 subjects will have died.

Among all subjects (ESR1-mut and ESR1-mut-nd), the study will have 60% power to detect a hazard ratio of 0.75 at a 1-sided alpha level of 2.5%. Assuming a median OS of 25 months for the SOC treatment group, this hazard ratio represents a median OS of 33 months for the elacestrant treatment group. This calculation also accounts for 1 interim analysis at an information fraction of 0.4 with an alpha spending equal to 0.0001 at the interim analysis.

The study has enrolled 228 ESR1-mut subjects. Approximately 114 OS events are expected among the ESR1-mut subjects at the time of the second analysis of OS. With 114 OS events, the study will have 39% power to detect a hazard ratio of 0.73 at a 1-sided alpha level of 2.5%. Assuming a median OS of 28 months for the SOC treatment group, this treatment effect represents a median OS of 38 months for the elacestrant treatment group, an increase of approximately 10 months among the ESR1-mut subjects. This calculation also accounts for 1 interim analysis at an information fraction of 0.4 with an alpha spending equal to 0.0001 at the interim analysis.

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

4.2.7 Subpopulations

Subgroup analyses of IRC-assessed PFS, OS, ORR, DoR, and CBR will be performed in the same manner as the analyses using the ITT population for ESR1-mut subjects and for all subjects (ESR1-mut and ESR1-mut-nd) for the following stratification factors (based on eCRF):

- Prior treatment with fulvestrant (yes vs no)

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- Presence of visceral metastasis (yes vs no)

Subgroup analyses of IRC-assessed PFS, OS, ORR, DoR and CBR will also be performed in the same manner as the analyses using the ITT population for ESR1-mut subjects and all subjects (ESR1-mut and ESR1- mut-nd) by categories of

- Age (<65 years vs ≥65 years)
- Age (<75 years vs ≥75 years)
- Race (Caucasian vs Asian vs Other)
- Region (Europe [EU], North America [NA], Asia, Other)
- Baseline ECOG Performance Status (0 vs 1)
- Measurable disease at baseline (yes vs no)
- Number of prior lines of endocrine therapy in the advanced/metastatic setting (1 vs 2)
- Number of lines of chemotherapy in the advanced/metastatic setting (0 vs 1)

4.2.8 Withdrawals, Dropouts, Lost to Follow-up

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 was to 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.

4.2.9 Missing, Unused, and Spurious Data

Unless otherwise specified, missing dates for onset of AEs and start dates of concomitant medications will be handled according to the Missing Date Imputation Method in Appendix 7.1.

4.2.10 Visit Windows

CRF visits will be used for analysis. For the safety analysis, in the case of multiple observations at a specific visit, the observation which is the latest will be used. If more than one observation is made on the same day, an average value if continuous or the worst value if categorical will be included in the analysis.

4.3 Interim Analyses

At about 70% enrollment, an interim futility analysis will be provided to the IDMC. At that time, the total number of PFS events is expected to be around 119 (35% of the total events). At this interim data

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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 to check consistency for 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 ≥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%
- Other (specified in IDMC charter)

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.

The graphical display using predicted interval plots (PIPS) may be used to support the finding from the conditional power.

Details of statistical methods for the interim futility analysis are provided in the interim SAP Version 1.0 dated 17 August 2020.

4.4 Subject Disposition

Subject disposition will be tabulated by treatment group (elacestrant vs SOC) and by SOC type (fulvestrant vs AIs) to include the number screened, the number randomized, the number treated, the number in each subject population for data analysis, the number remaining on treatment, the number who discontinued study drug and the primary treatment termination reason as recorded in the eCRF, and the number who discontinued the study as well as the primary reason for study withdrawal as recorded in the eCRF.

A by-subject data listing of study drug information including the primary reason for treatment discontinuation and study withdrawal as recorded in the eCRF, if applicable, will be presented.

4.5 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group (elacestrant vs SOC) and by SOC type (fulvestrant vs AIs) using the ITT, RE, CBE and PP populations for ESR1-mut subjects and all subjects (ESR1-mut and ESR1-mut-nd). Age, age group (in years; <50; ≥50 and <65; ≥65 and <75; ≥75; in addition, <65 vs ≥65), height, weight (baseline), body mass index (BMI), race, sex, ethnicity, baseline disease characteristics, and ECOG performance status will be summarized using descriptive statistics. BMI is calculated as Weight (kg) / Height (m)^2, using baseline weight measurements.

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Baseline ESR1 mutation data per central laboratory results will be summarized by treatment group (elacestrant vs SOC) and by SOC type (fulvestrant vs AIs) using the ITT, RE, CBE and PP populations for ESR1-mut subjects. Number of subjects with each ESR1 mutation and number of ESR1 mutations per subject (0, 1, 2, 3, >3) will be summarized using descriptive statistics. A by-subject listing will be provided.

A summary of stratification factors at randomization in interactive randomization technology (IRT) system will be provided, including ESR1 mutation status detected by ctDNA (ESR1-mut vs ESR1-mut-nd), prior treatment with fulvestrant (yes vs no), and presence of visceral metastases (yes vs no). Stratification factors as recorded in the eCRF will also be summarized. Analysis of primary and secondary efficacy endpoints will adjust for the randomization stratification factors obtained from the eCRF.

No formal hypothesis testing will be performed.

4.6 Medical History, Disease History and Prior Therapies

Medical history will be presented by MedDRA (version 23.0) system organ class and preferred term (PT), summarizing by treatment group (elacestrant vs SOC) and SOC type (fulvestrant vs AIs) using ITT population for ESR1-mut subjects and all subjects (ESR1-mut and ESR1-mut-nd).

The following summaries will be provided by treatment group and SOC type for the ITT, RE, CBE and PP populations for ESR1-mut subjects and all subjects (ESR1-mut and ESR1-mut-nd):

Summary of breast cancer history and baseline disease characteristics will include years since diagnosis, stage at initial diagnosis, TNM staging at initial diagnosis, stage at baseline, TNM staging at baseline, sites of disease and number of metastatic sites (0, 1, 2, ≥3). Sites of disease will be categorized as breast, bone, bone only, visceral (any, and brain, liver, lung) and other.

Data on breast cancer diagnosis, hormone receptor status and HER2 status are based on local historical results. Summary of breast cancer histopathology will include source of tissue (original diagnosis, most recent biopsy, or interim time point), histology and grade, results for ER status including immunohistochemistry (IHC) percentage, results for progesterone receptor status including IHC percentage, results for HER2 status including IHC result and in situ hybridization (ISH) HER2/CEP17 ratio, if performed. Local historical data, including tissue source and results, for ESR1 and PIK3CA mutations will be summarized.

Summary of prior systemic anticancer therapies will include:

- Number of subjects with neoadjuvant therapy
- Number of subjects with adjuvant therapy
- Number of subjects with neoadjuvant and/or adjuvant (neo/adjuvant) endocrine therapy, and each type of endocrine therapy in neo/adjuvant setting
- Number of subjects with neo/adjuvant chemotherapy

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- Number of subjects with neo/adjuvant targeted therapy
- Total duration of AI therapy in any setting
- In advanced/metastatic setting
    - Number of lines of endocrine therapy (1 or 2) with documented progression
    - Best response to last line of endocrine therapy
    - Number of lines of chemotherapy (0 or 1)
    - Number of lines of targeted therapy
    - Number of subjects with each type of endocrine therapy
    - Number of subjects with each type of targeted therapy
- Time from last prior systemic anticancer therapy to randomization
- Number of subjects with each type of endocrine responsiveness status (primary resistance, secondary resistance, endocrine therapy sensitive)

Endocrine therapy includes fulvestrant, letrozole, anastrozole, exemestane and tamoxifen. AI therapy is a subset of endocrine therapy, including letrozole, anastrozole and exemestane. Targeted therapy includes mTOR inhibitor, PI3K inhibitor and VEGF inhibitor. Chemotherapy includes cytotoxic chemotherapy. Any setting includes neoadjuvant, adjuvant and advanced/metastatic combined.

According to the European Society for Medical Oncology (ESMO) guidelines, primary endocrine resistance is defined as relapse < 24 months while on endocrine therapy in adjuvant setting or progression < 6 months while on endocrine therapy in advanced/metastatic setting. Secondary endocrine resistance is defined as relapse ≥ 24 months while on endocrine therapy in adjuvant setting or progression < 12 months after end of endocrine therapy in adjuvant setting or progression ≥ 6 months while on endocrine therapy in advanced/metastatic setting. Endocrine sensitive is defined as relapse ≥ 12 months after end of endocrine therapy in adjuvant setting or progression ≥12 months after end of endocrine therapy in advanced/metastatic setting.

If a subject received multiple lines of AI therapy, duration of AI therapy includes the total number of calendar days using any AI therapy. Multiple AI therapies given on same day, will be counted as 1 day.

Summary of prior radiation therapy will include time from last therapy to first dose of study drug, body location(s), treatment setting category and primary reason for discontinuation.

Summary of breast cancer procedures will include time from last procedure to first dose of study drug, type of procedure(s) and treatment setting.

Post-treatment systemic breast cancer therapy will be presented in data listings. Number of subjects with post-treatment systemic breast cancer therapy will be summarized. Time to post-treatment systemic breast cancer therapy is defined as the number of days from date of last dose of study drug to initiation of systemic breast cancer therapy and will be summarized by category of systemic anticancer therapy (e.g., endocrine therapy, targeted therapy, etc.) and treatment group descriptively for the subjects who receive systemic breast cancer therapy after study drug discontinuation.

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4.7 Efficacy Evaluation

PFS and OS will be analyzed based on ITT population. ORR and CBR will be analyzed using RE population, and CBE population, respectively.

Final analysis of primary endpoints will be performed when approximately 160 events of objective disease progression or death based on IRC assessment have occurred among the ESR1-mut subjects and 340 events have occurred among all subjects (ESR1-mut and ESR1-mut-nd).

Analysis of primary and secondary efficacy endpoints will adjust for the randomization stratification factors (obtained from eCRF). For the analyses of all subjects, these stratification factors include ESR1-mutational status (ESR1-mut vs ESR1-mut-nd), prior treatment with fulvestrant (yes vs no), and presence of visceral metastases (yes vs no). For the analyses of ESR1-mut subjects, the stratification factors include prior treatment with fulvestrant (yes vs no) and presence of visceral metastases (yes vs no).

4.7.1 Primary Efficacy Endpoints

4.7.1.1 Primary Analysis

The primary efficacy endpoints of this study are

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

which will be analyzed using the ITT population for the ESR1-mut subjects, and all subjects (ESR1-mut and ESR1-mut-nd), respectively.

PFS is defined as the duration (in months) from the date of randomization to the earliest date of documented disease progression (RECIST v1.1) as assessed by the blinded IRC, or death due to any cause regardless of whether the subject withdraws from randomized therapy (i.e., date of PFS event or censoring – date of randomization + 1). Subjects who receive any new systemic anticancer therapy before disease progression will be censored at the date of the last adequate tumor assessment before initiation of new systemic anticancer therapy.

Tumor assessment visits are scheduled every 8 weeks ± 7 days. Subjects without documented progression or death will be censored at the date of last adequate tumor assessment. Subjects without any post-baseline tumor assessments will be censored at the date of randomization (i.e., Day 1); however, if the subject dies within 2 visits of baseline without any post-baseline tumor assessments, this will be counted as an event. If the subject progresses or dies immediately after 2 or more consecutive missed visits, the subject will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the 2 missed visits (Note: a visit with a response of NE is not considered as missed visit). Given the scheduled visit assessment scheme (i.e., every 8 weeks ± 7 days), 2 missing visits will equate to 18 weeks since the previous RECIST assessment, allowing for early and late visits (i.e., 2 x 8

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weeks + 1 week for an early assessment + 1 week for a late assessment = 18 weeks). Detailed censoring rules are described in Table 2.

Table 2 Rules for Deriving Date of Progression or Censor for PFS

Situation	Date of Progression/Death or Censoring	PFS 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) [1]	Date of last adequate tumor assessment	Censored
Subject lost to follow-up (or withdrew consent) before documented progression or death [1]	Date of last adequate tumor assessment	Censored
Documented progression [2]	Date of documented progression	Progressed
Death without documented progression [1]	Date of death	Progressed
Documented progression or death after missing 1 post-baseline tumor assessment [2]	Date of documented progression or death	Progressed
Documented progression or death after missing ≥2 consecutive post-baseline tumor assessments [2]	Date of last adequate tumor assessment before missed assessments or date of randomization, whichever is later	Censored

Note: If more than 1 situation applies, date of PFS and associated outcome will be determined by the earliest date and associated outcome above.

[1] If a subject received new systemic anticancer therapy, PFS will be censored at the date of last adequate tumor assessment before or on initiation of new systemic anticancer therapy.

[2] If progression occurred after initiation of new systemic anticancer therapy, PFS will be censored at the date of last adequate tumor assessment before or on initiation of new systemic anticancer therapy.

Kaplan-Meier method will be used to estimate the survival distribution function of PFS. The following summaries by treatment group will be provided: median PFS and 95% CI, 1st and 3rd quartiles and 95% CI, PFS rates and 95% CI at months 3, 6, 12 (and every 6 months thereafter until the end of follow-up or no more subjects are at risk). Confidence interval will be constructed using Brookmeyer and Crowley method (1982) via linear transformation.

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The difference in the primary endpoints between the 2 treatment groups will be analyzed using the stratified log-rank test, with the randomization stratification factors (as described in section 4.7) for generation of the p-value.

The hazard ratio (HR) and 95% CI for the treatment effect will be estimated using the stratified Cox proportional hazards regression model with Effron method of handling ties, stratified by randomization stratification factors (as described in section 4.7). Confidence interval will be constructed using the profile likelihood method.

The Kaplan–Meier curve of PFS of the 2 treatment groups will be displayed graphically, along with median event times and 95% CIs, for 2 sets of study subjects, ESR1-mut subjects and all subjects.

4.7.1.2 Assumptions of Proportionality

The assumption of proportional hazards will be tested first by examining Kaplan–Meier curves and plots of the log of negative log of estimated survival probability versus log (time) and, if these raise concerns, by fitting a time dependent covariate (adding a treatment-by-time or treatment-by-ln(time) interaction term) to assess the extent to which this represents random variation.

If a lack of proportionality is evident, the HR from the primary analysis can still be meaningfully interpreted as an average HR over time unless there is extensive intersection of the survival curves.

In addition, the Restricted Mean Survival Time (RMST) method (Royston and Parmar 2013) permits inference over a specified time period, with an area-under-the-curve type approach, in situations with non-proportional hazards. Details for RMST are described in the section of sensitivity and supplemental analysis below.

4.7.1.3 Sensitivity Analyses

The following sensitivity analyses will be performed.

Sensitivity Analysis 1 (Actual event PFS analysis): In this analysis, PFS events recorded after missing 2 or more consecutive tumor assessments will be included as events, with the PFS event date defined as the actual event date after the 2 missed tumor assessments.

Sensitivity Analysis 2 (Backdating PFS analysis): In this analysis, PFS events recorded after missing 2 or more consecutive tumor assessments will be included as events, with the PFS event date defined as the date of the next scheduled tumor assessment after the last adequate tumor assessment.

For example, suppose a subject had the last adequate tumor assessment in January, missed tumor assessments in March and May, and then had a PFS event in July. In Sensitivity Analysis 1, the subject will have the actual PFS event date in July as the event date; in Sensitivity Analysis 2, this subject will have the next scheduled tumor assessment date (after the last adequate tumor assessment in January) in March as the event date.

The above 2 sensitivity analyses will be performed in the same manner as the primary efficacy analyses.

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Sensitivity Analysis 3 (Unstratified analysis): As a sensitivity analysis to assess the impact of stratification (obtained from eCRF), the 2 treatment groups will be compared using the unstratified log-rank test. The HR together with the associated 95% confidence interval obtained using the unstratified Cox regression model will also be presented.

Sensitivity Analysis 4 (COVID-19 analysis): To assess potential COVID-19 impact, if subjects died due to COVID-19 infection without PD, PFS date will be censored at the death date. Analysis of PFS will be performed in the same manner as the primary efficacy analyses if at least 5% of deaths are due to COVID-19 infection.

Sensitivity Analysis 5 (Per-Protocol Population analysis): This analysis will be performed based on PP population in the same manner as the primary efficacy analyses if the primary endpoints are statistically significant.

4.7.1.4 Restricted Mean Survival Time Analysis

The RMST methodology is independent of the proportional hazards assumption and can be used as a supplemental analysis to explore the robustness of the primary analysis results. The restricted mean survival time is a measure of average survival from time 0 to a specified time point (τ) and is estimated as the area under the survival curve up to that point. It is noted that the truncation time point (τ) should not exceed the minimum of the largest follow-up time for both treatment groups so that the RMST of both treatment groups being evaluated can be adequately estimated and comparison between treatments is feasible; τ should be clinically meaningful and closer to the end of the study follow-up so that the majority of survival outcomes will be covered by the time interval. The RMST up to time τ can then be interpreted as the expected survival time restricted to the common follow-up time τ among all patients.

The RMST analysis of the primary efficacy endpoints will be performed with the randomization stratification factors (as described in section 4.7) as covariates.

RMST estimate of the IRC-assessed PFS with the 95% CI will be provided for each treatment group. The treatment effect will be assessed based on the difference of RMST in IRC-assessed PFS between the treatment groups. The associated 95% CI for the difference in means and a p-value will be generated.

4.7.2 Key Secondary Efficacy Endpoints

4.7.2.1 Key Secondary Analysis

Key secondary efficacy endpoints include the following:

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

Overall survival is defined as the time from the date of randomization until death due to any cause regardless of whether the subject withdraws from randomized treatment or receives another anticancer therapy (i.e., date of death or censoring – date of randomization + 1). Any subject not known

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to have died at the time of analysis will be censored based on the last recorded date on which the subject was known to be alive. The last known alive date is the date subject last confirmed to be alive from eCRF Survival Status page.

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 each of the 2 sets of study subjects, OS will be analyzed at the following 2 time points

- At the time of the primary 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, and
- At the time of the final OS analysis (when approximately 50% of the subjects have died)

At each time point, analyses of OS will be conducted in a similar manner as the primary analysis of PFS. Number and percentage of subjects with event and subjects censored will be tabulated by treatment group.

Kaplan-Meier method will be used to estimate the survival distribution function of OS. The following summaries by treatment group will be provided: median OS and 95% CI, 1st and 3rd quartiles and 95% CI, overall survival rates and 95% CI at months 6, 12, and 18 (and every 6 months thereafter until the end of follow-up or no more subjects are at risk).

The difference in the key secondary endpoints between the 2 treatment groups will be analyzed using the stratified log-rank test, with the randomization stratification factors (as described in section 4.7) for generation of the p-value.

The HR and 95% CI for the treatment effect will be estimated using the stratified Cox proportional hazards regression model with Efron method of handling ties, stratified by randomization stratification factors (as described in section 4.7). Confidence interval will be constructed using the profile likelihood method.

The Kaplan–Meier curve of OS of the 2 treatment groups will be displayed graphically, along with median event times and 95% CIs, for 2 sets of study subjects, ESR1-mut subjects and all subjects (ESR1-mut and ESR1-mut-nd).

4.7.2.2 Sensitivity Analyses

A sensitivity analysis for OS will examine the censoring patterns to rule out attrition bias with regard to the treatment comparisons, achieved by a Kaplan-Meier plot of time to censoring where the censoring indicator of OS is reversed.

The number of subjects prematurely censored will be summarized by treatment group. A subject would be defined as prematurely censored if their survival status was not defined at the data cut-off (DCO).

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In addition, duration of follow-up will be summarized using medians:

- In all subjects: Time from randomization to the date of death (i.e. overall survival) or to the date of censoring (date last known to be alive) for censored subjects regardless of treatment group.
- By treatment group: Time from randomization to the date of death (i.e. overall survival) or to the date of censoring (date last known to be alive) for censored subjects

To assess potential COVID-19 impact, if subjects died due to COVID-19 infection, OS date will be censored at the death date. Analysis of OS will be performed in the same manner as the primary key secondary analysis if at least 5% of deaths are due to COVID-19 infection.

4.7.2.3 Restricted Mean Survival Time Analyses

Restricted mean survival time analysis will be provided for the key secondary efficacy endpoints in a similar manner as IRC-assessed PFS as described in Section 4.7.1.4 as a supportive analysis.

4.7.3 Other Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be assessed in ESR1- mut-nd subjects

- IRC-assessed PFS
- OS

The following secondary efficacy endpoints will be assessed for ESR1-mut subjects, ESR1- mut-nd subjects, and All (ESR1-mut and ESR1- mut-nd) subjects:

- 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 efficacy 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 all subjects (ESR1-mut and ESR1- mut-nd).

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4.7.3.1 Local Investigator-assessed PFS

PFS will also be derived based on local investigator assessment, in the same way as the derivation of the primary endpoints and will be analyzed using the ITT population for ESR1-mut subjects, ESR1- mut-nd subjects, and all subjects (ESR1-mut and ESR1- mut-nd), in the same manner as the primary and secondary analyses.

4.7.3.2 IRC-assessed Objective Response Rate (ORR)

Independent Review Committee-assessed ORR is defined as the percentage of subjects whose best overall response (BOR) was either complete response (CR) or partial response (PR), where BOR will be derived using blinded IRC assessment following the RECIST (version 1.1) criteria. For each subject, BOR can be 1 and only 1 of the following: CR, PR, stable disease (SD), progressive disease (PD) and not evaluable (NE), with derivation using the order of CR > PR > SD > PD > NE. Additionally, the response of CR or PR will require confirmation at least 4 weeks after the initial documentation of the response. When confirmation is required, BOR is derived according to Table 3 below. Responses recorded after initiation of new systemic anti-cancer therapy will be excluded from BOR derivation.

Table 3 Best Overall Responses when Confirmation of CR and PR 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, other~~wise, 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, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable.
[a] If a CR is truly met at 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 (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may have been claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first timepoint.

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Overall response First time point	**Overall response Subsequent time point**	**Best overall response**
Under these circumstances, the original CR should be changed to PR and the best response is PR.		

Independent Review Committee-assessed ORR derived as above, will be summarized using the RE population (defined based on IRC assessment) for ESR1-mut subjects, ESR1- mut-nd subjects, and all subjects (ESR1-mut and ESR1- mut-nd). The ORR will be summarized as a binomial response rate with 95% CIs based on Clopper-Pearson method. Comparison between treatment groups will be performed using Cochran-Mantel-Haenszel (CMH) test adjusting for randomization stratification factors (as described in section 4.7). The Mantel-Fleiss criterion will be checked to verify the suitability of CMH test. If Mantel-Fleiss criterion ≤5 (which might happen with a large number of small strata), an exact test (Proc Logistic) will be used instead with adjustment for the same set of randomization stratification factors.

Difference between treatment groups in the ORR along with 95% stratified Newcombe confidence limits for CI will also be provided.

A waterfall plot will be produced to present percentage change from baseline in sum of the diameters and BOR for each subject by treatment group.

4.7.3.3 IRC-assessed Duration of Response (DoR)

Independent Review Committee-assessed DoR will be summarized using the RE population (based on IRC assessment) who achieved confirmed CR or PR based on the blinded IRC review for ESR1-mut subjects, ESR1- mut-nd subjects, and all subjects (ESR1-mut and ESR1- mut-nd).

Duration of Response is defined as the duration from the first response until disease progression or death from any cause. DoR will be censored at the last assessment if the subject did not have disease progression. If subjects receive new systemic anti-cancer therapy before progression, DoR will be censored at the last assessment before or on the date of initiation of new systemic anti-cancer therapy. In addition, subjects who have PD or death after ≥2 missing tumor assessments will be censored at the last tumor assessments prior to the missed visits.

Duration of Response will be analyzed by treatment group using the Kaplan-Meier method, with the median, 25th and 75th percentiles reported along with the 95% CIs. The Kaplan–Meier curve will also be plotted by treatment group.

4.7.3.4 IRC-assessed Clinical Benefit Rate (CBR)

Independent Review Committee-assessed CBR will be summarized using the CBE population (based on IRC assessment) for ESR1-mut subjects, ESR1- mut-nd subjects, and all subjects (ESR1-mut and ESR1-mut-nd). CBR is defined as the proportion of subjects who had confirmed CR or PR any time during the study, or SD that lasted at least 24 weeks (including disease assessments performed up to a week

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earlier than the scheduled date). The IRC-assessed CBR will be derived based on the blinded IRC assessment and will be analyzed in the same manner as the analysis of ORR.

4.7.3.5 Local Investigator-assessed ORR and DoR

Objective Response Rate will be derived from tumor assessments performed by Local Investigators using the RECIST criteria and analyzed in the same manner as the analysis of IRC-assessed ORR.

Local Investigator-assessed DoR will be derived and analyzed in the same manner as the IRC-assessed DoR.

Analyses of local Investigator-assessed ORR and DoR will be provided for the RE population (based on Local Investigator assessment) for ESR1-mut subjects, ESR1- mut-nd subjects, and all subjects (ESR1-mut and ESR1- mut-nd).

4.7.3.6 Local Investigator-assessed CBR

The Local Investigator-assessed CBR will be derived based on Local Investigator assessment, similar to the derivation of the IRC-assessed CBR and analyzed in the same manner for CBE population (based on Local Investigator assessment) for ESR1-mut subjects, ESR1- mut-nd subjects, and all subjects (ESR1-mut and ESR1- mut-nd).

4.7.4 Subgroup Analyses

Subgroup analyses of IRC-assessed PFS, OS, ORR, DoR, and CBR will be performed in the same manner as the analyses using the ITT population for ESR1-mut subjects and all subjects (ESR1-mut and ESR1-mut-nd) for the following stratification factors (based on eCRF):

- Prior treatment with fulvestrant (yes vs no)
- Presence of visceral metastasis (yes vs no)

Subgroup analyses of IRC-assessed PFS, OS, ORR, DoR and CBR will be performed in the same manner as the analyses using the ITT population for ESR1-mut subjects and all subjects (ESR1-mut and ESR1-mut-nd) for the following subgroups:

- Age (<65 years vs ≥65 years)
- Age (<75 years vs ≥75 years)
- Race (Caucasian vs Asian vs Other)
- Region (Europe [EU], North America [NA], Asia, Other)
- Baseline ECOG Performance Status (0 vs 1)
- Measurable disease at baseline (yes vs no)
- Number of prior lines of endocrine therapy in the advanced/metastatic setting (1 vs 2)
- Number of lines of chemotherapy in the advanced/metastatic setting (0 vs 1)

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A subgroup analysis may not be performed if the number of subjects in the subgroup in each treatment group is not sufficiently large (e.g., <5%). In the case of the subgroup variable with more than 2 levels, pooling may be considered when there is insufficient sample size within the level.

4.8 Patient Reported Outcomes (PROs)

PRO endpoints are secondary endpoints and will be summarized by treatment group using the ITT population for ESR1-mut subjects and all subjects (ESR1-mut and ESR1- mut-nd).

4.8.1 EQ-5D-5L

The EQ-5D-5L will be used to explore the impact of treatment and disease state on health state utility.

The EQ-5D-5L, developed by the EuroQol Group, is a generic questionnaire that provides a simple descriptive profile of health and a single index value for health status for economic appraisal. The EQ-5D-5L questionnaire comprises 6 questions that cover 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). For each dimension, respondents select which statement best describes their health on that day from a possible 5 options of increasing levels of severity (no problems, slight problems, moderate problems, severe problems and unable to/extreme problems). A unique EQ-5D health state, termed the EQ-5D-5L profile, is reported as a 5-digit code with a possible 3,125 health states. For example, state 11111 indicates no problems on any of the 5 dimensions. Respondents also assess their health on that day using the EQ-VAS, which ranges from 0 (worst imaginable health) to 100 (best imaginable health).

The EQ-5D profile will be converted into a weighted health state utility value, termed the EQ-5D index, by applying a country-specific equation to the EQ-5D-5L profile that represents the comparative value of health states. This equation is based on national valuation sets elicited from the general population and the base case will be the UK perspective. Where a valuation set has not been published, the EQ-5D-5L profile will be converted to the EQ-5D index using a crosswalk algorithm (van Hout et al. 2012). The EQ-VAS is reported separately.

Descriptive statistics will be calculated for each scheduled visit/time point in the study, for each study drug, and as a total. This will report the number of subjects, the number of EQ-5D questionnaires completed for each visit, and the number and proportion of subjects responding to each dimension of the EQ-5D-5L. Additionally, summary statistics (eg, n, mean, median, SD, min, and max) will be reported for the EQ-5D index score and the EQ-VAS score, and the change from baseline will be reported for the EQ-5D index score and the EQ-VAS score.

Graphical plots of the mean (+/- standard deviation) EQ-5D index score and EQ-VAS score, including change from baseline by scheduled visits/time points in the study may be produced.

4.8.2 EORTC-QLQ-C30

The EORTC QLQ-C30 consists of 30 questions that can be combined to produce 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting),

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and global health status/QoL scale. The EORTC QLQ-C30 will be scored according to the EORTC QLQ-C30 Scoring Manual (Fayers et al. 2001). An outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales, each of the functional scales, and the global measure of health status scale in the EORTC QLQ-C30 according to the EORTC QLQ-C30 Scoring Manual. Higher scores on the global measure of health status and functional scales indicate better health status/function, but higher scores on symptom scales represent greater symptom severity.

Patient-reported outcome (PRO), based on scales from the QLQ-C30 questionnaires, will be summarized at Cycle 1 Day 1 (i.e., baseline) and each time it is measured according to the protocol schedule, along with change from baseline (CFB). Line graph presentation of arithmetic mean (±standard deviation) plots of scores and change from baseline versus time point will be produced.

The following scores will be calculated: 5 functional scales, 3 symptom scales, a global health status/quality of life (QoL) scale, and 6 single items, Table 4.

Table 4 EORTC QLQ-30 Scales and Items

Scale/Item	Label	Items (Questions) included	Range of response for items
Global Health Status / QOL	QL2	29, 30	6
Functional Scales			
Physical functioning	PF2	1 - 5	3
Role functioning	RF2	6, 7	3
Emotional functioning	EF	21 - 24	3
Cognitive functioning	CF	20, 25	3
Social functioning	SF	26, 27	3
Symptom Scales/Items			
Fatigue	FA	10, 12, 18	3
Nausea and vomiting	NV	14, 15	3
Pain	PA	9, 19	3

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Scale/Item	**Label**	**Items (Questions) included**	**Range of response for items**
Dyspnea	DY	8	3
Insomnia	SL	11	3
Appetite loss	AP	13	3
Constipation	CO	16	3
Diarrhea	DI	17	3
Financial difficulties	FI	28	3

All of the scales and single-item measures range in score from 0 to 100. For global health status and functional scales, 100 is associated with a high performance while for symptoms scales, 100 is associated with high burden related to the symptoms. The calculation for each score is derived as follows.

1. A raw score is calculated as the average of the items of the scale
2. A linear transformation is applied to standardize the raw score so that the score ranges from 0 to 100.

For example, the below algorithm demonstrates how various QLQ-C30 scales are computed:

Functional scales/items: Score = {1-(RS-1)/range}×100

Symptom scales/items: Score = {(RS-1)/range}×100

Global health status/QoL: Score = {(RS-1)/range}×100

For all scales, the Raw Score, RS, is the mean of the component items.

In case of missing items, the following rules will be applied:

1. If at least half of the items from the scale are not missing, missing items will be ignored. RS will be calculated as the mean of the non-missing items.

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2. If not, the scale will be set to missing. For single item measures, the score is set to missing.

QoL endpoints will be summarized by treatment at baseline and each study visit, along with CFB. Line graph presentation of arithmetic mean (±standard deviation) plots of scores and CFB versus time point will be produced.

Summaries of absolute and change from baseline values of each EORTC QLQ-C30 scale/item and associated 95% CI will be reported by scheduled visit for each treatment group. Line graph presentation of least square mean plots of scores versus time point will be produced.

4.8.3 PRO-CTCAE

The patient reported outcomes version of the common criteria for adverse events (PRO-CTCAE), a PRO version of the CTCAE system developed by the National Cancer Institute (NCI), is included to assess tolerability from the patient's perspective. It was developed in recognition that collecting symptom data directly from patients can improve the accuracy and efficiency of symptomatic AE data collection. Symptoms have been converted to patient terms (e.g., CTCAE term "myalgia" converted to "aching muscles"). 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.

PRO-CTCAE data at baseline will be presented as the number (%) of subjects with each level of attribute item for each PRO-CTCAE symptom term. Change from baseline at all visits will be presented in 3 categories: improved, no change or worsened from baseline for each PRO-CTCAE symptom term. A bar chart of the incidence by visit will be presented for each symptom term.

4.8.4 Sensitivity Analyses

Sensitivity analyses will be performed for all PRO endpoints by excluding subjects who had at least 1 missing visit due to COVID-19. Sensitivity analyses will be performed in the same manner as the primary PRO analyses.

4.8.5 Exploratory Analyses

A mixed model repeated measures (MMRM) model may be developed to analyze the CFB of QoL over study visits through Cycle 6. Subjects in the ITT population having at least a baseline value and one value after randomization should be included in this analysis. The model may consider CFB as the dependent variable and include the following variables: treatment, visit, stratification factors, baseline value, interaction of visit and baseline, interaction of treatment and visit. Subject will be a random effect. Least square means and their 95% confidence intervals may be computed. Line graph presentation of least square mean plots of scores versus time point may be produced.

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4.9 Pharmacokinetic Evaluations

Elacestrant plasma concentrations will be summarized descriptively (with n, mean, standard deviation, CV, median, minimum, maximum, geometric mean and its associated CV) by visit and nominal timepoint (pre-dose or 4 hours post-dose) for ESR1-mut subjects, all subjects (ESR1-mut and ESR1-mut-nd) and ESR1-mut-nd subjects. Plot of geometric mean of the elacestrant concentrations by nominal time point will also be presented.

4.10 Exploratory Analysis

Time to Chemotherapy (TTC) is defined as the number of days from randomization to initiation of chemotherapy and will be summarized by treatment group descriptively for the subjects who receive chemotherapy as first systemic anticancer therapy after treatment discontinuation.

Listings will be provided for tumor biopsies obtained at pre-treatment, on-treatment and post-treatment periods.

Biomarker analyses may be conducted when study is closed.

4.11 Independent Data Monitoring Committee

An independent IDMC external to both the Sponsor and 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. IDMC responsibilities and review schedules are outlined in an IDMC charter.

4.12 Safety Analyses

Unless otherwise specified, safety analyses will be conducted using the Safety population for ESR1-mut subjects and all subjects (ESR1-mut and ESR1- mut-nd). Safety evaluations will be based on the incidence, relationship, severity grade, and seriousness of treatment emergent adverse events (TEAEs), ECOG performance status, vital signs, ECGs, and laboratory tests of chemistry, hematology, and coagulation parameters, as well as dose modifications (interruptions/reductions) due to TEAEs, and treatment discontinuations due to TEAEs. In addition, study drug exposure and usage of concomitant medications will be summarized.

4.12.1 Treatment Exposure

Treatment exposure will be summarized descriptively by treatment group and SOC type (fulvestrant vs AIs) as duration on treatment and extent of exposure to study drug.

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Duration on Treatment will be defined as follows:

Treatment duration (days) for elacestrant and AIs will be calculated as (Last dose date – First dose date + 1).

Treatment duration (days) for fulvestrant will be calculated as (End date of last cycle – First dose date + 1). End date of last cycle is the earliest of the following dates: the expected end date of last cycle, date of death, date of last known alive, date of subject withdrawal from the study, or the analysis cut-off date if subject is known to be alive after analysis cut-off date. Expected end date of last fulvestrant cycle is calculated as:

- If last dose of fulvestrant was administered in cycle 1, expected end date of last cycle is the last dose date + 13 days
- If last dose of fulvestrant was administered beyond cycle 1, expected end date of last cycle is the last dose date + 27 days

Measures of extent of exposure include the Total Number of Doses per Subject, Absolute Dose Intensity, Relative Dose Intensity (%) and compliance (%).

Duration on Treatment, Total Number of Doses, Absolute Dose Intensity, Relative Dose Intensity and Compliance will be summarized by treatment and SOC type (fulvestrant vs AIs), as well as presented in a by-subject data listing.

4.12.1.1 Elacestrant/AIs

For subjects assigned to take the oral drugs of elacestrant and the AIs, the study drug is to be taken every day during treatment. The start and stop date will be recorded for each un-interrupted dosing period, where the same dose is taken every day. In case of a dose change, such as dose level change, or missing doses, etc, a new period will be recorded.

The number of doses in a period is the number of days in the period calculated as (end date – start date + 1), assuming one dose per day. The ***Total Number of Doses*** is then calculated by taking the sum of the number of doses in all the periods. Study drug ***Compliance*** is defined as *Total Number of Doses divided by Duration on Treatment.*

The dose intensity of a period is the sum of doses in the period divided by the number of days in the period calculated as (end date – start date + 1), assuming one dose per day. The '**Absolute Dose Intensity (mg/day)'** is then calculated by taking the sum of doses in all the periods divided by the sum of the number of days in each period. The '**Planned dose intensity (mg/day)'** for a subject is their initial dose. The '**Relative Dose Intensity (%)'** is Absolute Dose Intensity divided by planned dose intensity *100.

Dose Reductions

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Frequency tables on number of subjects with at least 1 dose reduction of any study drug will be provided.

Dose reductions due to AE for subjects receiving elacestrant will be summarized as follows:

- Number of subjects with at least 1 dose reduction
- Time to first dose reduction
- Number of dose reductions (0 vs 1 vs 2)

A listing with visit (cycle) dates, drug administration start and end dates and times, and end of study status will be provided. Subjects with missing or delayed doses will be listed.

4.12.1.2 Fulvestrant

For subjects assigned to take fulvestrant, the study drug is to be taken via intramuscular injection on Days 1, 15, 29, and every 28 days thereafter.

For these subjects, the ***Total Number of Doses*** is derived by taking the sum of the number of doses recorded during treatment.

Total Number of Intended Dose = 1, if *Duration of treatment* < 15

= 2, if 15 ≤ *Duration of Treatment* < 29

= round ([*Duration of Treatment-28] /* 28, 1) + 2

Compliance is defined as *Total Number of Doses* divided by the *Total Number of Intended Doses.*

Dose Reductions

Dose reductions due to AE for subjects receiving fulvestrant will be summarized as follows:

- Number of subjects with 1 dose reduction
- Time to first dose reduction

Number of missing doses due to COVID-19 will be summarized using descriptive statistics. Administration details due to COVID-19 will be presented in a by-subject listing.

4.12.2 Adverse Events

All AEs will be coded to preferred term (PT) and system organ class and using the MedDRA (version 23.0) coding dictionary.

Analyses of AEs will be performed for those events that are considered to be treatment-emergent adverse events (TEAEs), where TEAE is defined as:

- Any AE that was absent (i.e., had not occurred) or had resolved prior to the start of study drug, and which occurred on or after the date of the first dose of study drug and within 30 days of the last dose of study drug; or

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- Any AE that started prior to the first dose of study drug, was ongoing after treatment started, and increased in severity after the start of study drug and within 30 days of the last dose of study drug

Adverse events will be summarized by subject incidence rates; therefore, in any tabulation, a subject contributes only once to the count for a given system organ class or PT. Preferred terms for a similar medical concept (i.e., synonym terms) will be grouped across different system organ classes in all AE summary tables except as otherwise noted. All listings will present PTs by original PT term.

For summaries by severity/toxicity grade, a subject with multiple occurrences under the same PT or system organ class will be represented under the most severe occurrence. For summaries by relationship to study drug, a subject with multiple occurrences under the same PT or system organ class will be represented under the most related occurrence. A TEAE is considered treatment-related if its causality was related on the AE eCRF page.

The worst toxicity grade per subject, by system organ class, or per PT will be used in the CTCAE grade summary. Missing grade will be not imputed. Missing relationship to study drug will not be imputed.

An overall summary of AEs will include the number of subjects in the following categories:

- Any TEAE
- Any treatment-related TEAE
- Any CTCAE Grade 3 and Grade 4 TEAE
- Any treatment-related CTCAE Grade 3 and Grade 4 TEAE
- Any fatal (Grade 5) TEAE
- Any treatment-related fatal (Grade 5) TEAE
- Any SAE
- Any treatment-related SAE
- Any TEAE leading to dose interruption
- Any treatment-related TEAE leading to dose interruption
- Any TEAE leading to dose reduction
- Any treatment-related TEAE leading to dose reduction
- Any TEAE leading to discontinuation of study drug
- Any treatment-related TEAE leading to discontinuation of study drug

TEAEs will also be summarized by system organ class, PT, treatment group and SOC type (fulvestrant vs AIs) for the following:

- All TEAEs
- Treatment-related TEAE

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- CTCAE Grade 3 and Grade 4 TEAEs
- Treatment-related CTCAE Grade 3 and Grade 4 TEAEs
- Fatal (Grade 5) TEAEs
- Treatment-related fatal (Grade 5) TEAEs
- SAEs
- Treatment-related SAEs
- TEAEs leading to dose interruption
- Treatment-related TEAEs leading to dose interruption
- TEAEs leading to dose reduction
- Treatment-related TEAEs leading to dose reduction
- TEAEs leading to discontinuation of study drug
- Any treatment-related TEAE leading to discontinuation of study drug

Summary TEAE tables described above (except SAEs) will be presented using grouped PTs as well. AE grouping will be provided in a supplementary document.

All AEs with outcome of death, all serious TEAEs and TEAEs leading to treatment discontinuation will be listed.

TEAEs will also be summarized by PT, treatment group and SOC type (fulvestrant vs AIs), by descending order of overall frequency in the elacestrant group.

A by-subject data listing of all the AEs will be provided by treatment group and SOC type (fulvestrant vs AIs). The listing will include subject, verbatim term, original PT, and system organ class, TEAE flag (yes/no), SAE flag (yes/no), the AE start and stop dates and study days, AE severity grade, relationship to study drug, actions taken, and outcome. The listing will also be provided for subjects <65 years and subjects ≥65 years separately.

In addition, summary of primary cause of death will be provided by treatment group and SOC type (fulvestrant vs AIs). A listing of all deaths will be provided, including primary cause of death.

4.12.3 Laboratory Data

Summaries of laboratory data using descriptive statistics by study visit will be presented by treatment and SOC type (fulvestrant vs AIs), including absolute results and changes from baseline. This includes chemistry, hematology, and coagulation. Results from unscheduled visits will not be included in this summary.

Laboratory values will be graded by NCI CTCAE v5.0, where applicable.

Shift analyses of chemistry, hematology, and coagulation laboratory data from baseline to the worst post-baseline value in CTCAE grade (when applicable) will be performed by treatment group and SOC

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type (fulvestrant vs AIs), where the baseline category and post-baseline category will be tabulated. In the shift tables, percentages will only be calculated based on the number of subjects that have valid data for both baseline and at least 1 post-baseline assessment; subjects who are missing either assessment will not be included in the percentage calculation (numerator or denominator). Results from both scheduled and unscheduled visits will be included in the shift analyses, as applicable.

A summary of subjects with abnormal liver function tests (LFTs) during treatment will be presented by maximum elevation of LFTs. Abnormal LFT criteria are summarized as follows:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3x upper limit of normal (ULN) and 3x baseline (CTCAE Grade 2 or above)
- ALT or AST > 5x ULN and 5x baseline (CTCAE Grade 3 or 4)
- ALT or AST > 20x ULN and 20x baseline (CTCAE Grade 4)
- ALT > 3x ULN and 3x baseline (CTCAE Grade 2 or above)
- ALT > 5x ULN and 5x baseline (CTCAE Grade 3 or 4)
- ALT > 20x ULN and 20x baseline (CTCAE Grade 4)
- AST > 3x ULN and 3x baseline (CTCAE Grade 2 or above)
- AST > 5x ULN and 5x baseline (CTCAE Grade 3 or 4)
- AST > 20x ULN and 20x baseline (CTCAE Grade 4)
- Serum total bilirubin >1.5x ULN and 1.5x baseline (CTCAE Grade 2 or above)
- Serum total bilirubin >2x ULN and 2x baseline
- Serum total bilirubin >3x ULN and 3x baseline (CTCAE Grade 3 or 4)
- Alkaline phosphatase >1.5x ULN and 1.5x baseline
- Alkaline phosphatase >3x ULN and 3x baseline
- ALT or AST >3x ULN and total bilirubin >2x ULN
- ALT or AST >3x ULN and total bilirubin >2x ULN, plus alkaline phosphatase <2x ULN

All laboratory data including results from unscheduled visits will be provided in data listings with indication of higher or lower than the associated normal range of each laboratory test.

4.12.4 Vital Signs

Vital sign data will be summarized by treatment group and SOC type (fulvestrant vs AIs) for each visit/time point. For vital signs, descriptive statistics will be provided for the observed values and for the corresponding change from baseline values. Results from unscheduled visits will not be included in this summary. However, vital sign data from all post-baseline assessment visits (scheduled and unscheduled) will be used for the abnormal value determination.

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Vital sign data will also be presented for each subject in a data listing.

Abnormal vital sign values

Values of vital signs are considered abnormal if they meet the selected criteria listed in Table 5 Appendix 8.2. The number (and percentage) of subjects with post-baseline abnormal values who did not have abnormal values at baseline will be analyzed by treatment group and SOC type (fulvestrant vs AIs) using the Safety population. For calculation of the percentages for each vital sign parameter, the denominator is based on the number of subjects who had no abnormal values at baseline and had at least 1 post-baseline assessment for the vital sign parameter being analyzed. The numerator is based on subjects from the denominator who had at least 1 abnormal value post baseline for the vital sign parameter being analyzed. A supportive listing of subjects with any abnormal values will also be provided.

4.12.5 Electrocardiogram

All ECGs will be performed in triplicate using central vendor ECG machine. On Cycle 1 Day 1 and Cycle 1 Day 15, ECGs will be performed pre-dose and 4 hours post-dose. Electrocardiograms at all other visits will be performed pre-dose only. Electrocardiogram parameters collected are Ventricular Rate (VR), PR-interval, QRS-duration, QT-interval, QTcF-interval (QT corrected by Fridericia's method, ie, $QT/RR^{0.33}$) and the Central Reader's assessment of the ECG profile.

The actual value and change from baseline will be summarized descriptively by treatment group and SOC type (fulvestrant vs AIs) for the quantitative ECG results by time point. Results from unscheduled visits will not be included in this summary. Overall ECG impression will be assessed by the Central Reader in 3 categories: normal, not clinically significant abnormal, or clinically significant abnormal. A listing of ECG interpretation will be provided.

The number and percentage of subjects with change from baseline >30 msec and >60 msec and the number and percentage of subjects with newly occurring value ≥450 msec in QT and QTcF will be presented by treatment group and SOC type (fulvestrant vs AIs). Shift tables from baseline to worst post-baseline value will be provided by treatment group and SOC type (fulvestrant vs AIs) for QT and QTcF values in the following categories: < 450 msec, ≥ 450 to ≤ 480 msec, > 480 to ≤ 500 msec, and > 500 msec.

A listing of subjects who experienced QTcF ≥450 at any time post-baseline, or experienced >30 msec increase from baseline at any time will be provided.

Sensitivity analyses will be performed for ECGs by excluding subjects who had at least 1 missing visit due to COVID-19. Sensitivity analyses will be performed in the same manner as the primary ECG analyses.

All ECG data for each subject will be provided in a data listing.

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4.12.6 Prior and Concomitant Medications

Concomitant medications will be coded using the WHO Drug Dictionary (version Sep2018). Results will be tabulated by anatomic therapeutic class (ATC), preferred term (PT), treatment and SOC type (fulvestrant vs AIs). Any medications that did not end prior to first dose of study drug will be included in the tabulation of concomitant medications. In addition, concomitant medications used to treat bone metastases (e.g., bisphosphonates, RANKL inhibitors) will be tabulated in the same manner.

Prior medications (i.e., those used prior to the initiation of study drug and ended prior to the first dose of study drug) will be summarized descriptively by ATC, PT, treatment group and SOC type (fulvestrant vs AIs).

All medications recorded on the concomitant medications log will be presented in a by-subject data listing.

Number and percentage of subjects with prohibited concomitant medications of moderate or strong CYP3A4 inhibitors or inducers will be summarized by treatment group and SOC type (fulvestrant vs AIs). A by-subject data listing will be provided.

Number and percentage of subjects who received any on-treatment palliative radiotherapy will be summarized by treatment group and SOC type (fulvestrant vs AIs), and will include indication, body site of radiation, AE resulting in need for radiotherapy, and number of subjects who had radiation therapy to target lesions and number of subjects who had radiation therapy non-target lesions. A by-subject listing will be provided.

All prior and concomitant therapies/procedures will be provided in a listing. Prior and concomitant transfusions will be summarized by transfusion type and by treatment group and SOC type (fulvestrant vs AIs). All prior and concomitant transfusions will be provided in a listing.

4.12.7 ECOG Performance Status

ECOG performance status is assessed at baseline, every cycle post baseline and at the End of Treatment (EOT) visit. ECOG performance status will be summarized over time by treatment group and SOC type (fulvestrant vs AIs) until the last cycle. Change from baseline to last cycle or EOT in ECOG performance will be summarized by treatment and SOC type (fulvestrant vs AIs) in a shift table.

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5 COVID-19 IMPACT

The COVID-19 worldwide pandemic has impacted the conduct of this study. Challenges led to issues such as quarantines, site closures, travel limitations, or interruptions to the supply chain of investigational products. These challenges may have led to difficulties in sites adhering to protocol-specified visits and/or procedures, including administration of investigational products.

Regulatory authorities in the EU and the US have provided guidance on how to handle the potential impacts of the COVID-19 pandemic when conducting clinical studies. In the US, the Food and Drug Administration (FDA) published "FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Public Health Emergency", and in the EU, the European Medicines Agency (EMA) published "Guidance on the Management of Clinical Trials during the COVID-19 (coronavirus) pandemic."

5.1 COVID-19 Overall Impact on Scheduled Assessments

Analyses of COVID-19 impact will be based on the "COVID-19 Impact on Visits," "COVID-19 Impacted visit assessments" and "COVID-19 Study/Treatment Discontinuation" eCRF pages.

COVID-19 overall visit impact will be tabulated for the ITT population. The number and percentage of subjects in the categories defined by COVID-19 impact on visit and COVID-19 reasons for impacted visit will be tabulated. Alternative methods of partially executed visits will be summarized. The number and percentage of subjects will be presented by alternative method and treatment group.

5.2 By-subject COVID-19 Listings

A by-subject listing of COVID-19 impacted visit assessments will be provided. Details of impacted visits will be listed.

5.3 By-Site and By-country COVID-19 Impact

COVID-19 impact will be tabulated for each site. The number and percentage of subjects who had at least 1 impacted visit due to COVID-19 will be presented by site and treatment group. COVID-19 impact will be also tabulated for each country in the same manner.

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6 CHANGES TO PLANNED ANALYSES

The following changes were made from RAD1901-308 Protocol Version 6.0 dated 25 March 2020 in this SAP dated 04MAY2021 Version final 1.1:

- The definitions of the analysis populations of Response Evaluable (RE) and Clinical Benefit Evaluable (CBE) have been updated in Section 3.
- The "the length of time from randomization until…" has been updated to "the time from randomization until…" in definition of OS and PFS in Section 1.2 to avoid redundancy.
- The protocol specified that "ORR and CBR will be summarized as a binomial response rate and compared between treatment groups using stratified Fisher's exact test." As there is no SAS procedure supporting stratified Fisher's exact test, the analysis method for ORR and CBR has been updated to CMH test and exact test (Proc Logistic) in Section 4.7.3.
- The protocol specified that "PK analyses will be performed using the PK population." One of the secondary objectives is to assess the PK of elacestrant. As there are only 2 PK time points, it is not possible to perform noncompartmental PK analyses. Instead, elacestrant plasma concentrations will be summarized as described in Section 4.9.
- The exploratory biomarker analyses will not be conducted.
- Per-protocol population has been added. It will be used in sensitivity analyses for PFS if primary endpoints are statistically significant.

The following change was made from SAP dated 05MAR2021 Version final 1.0 in this SAP dated 04MAY2021 Version final 1.1:

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

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7 REFERENCES

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8 CLINICAL STUDY REPORT APPENDICES

8.1 Missing Date Imputation Convention

8.1.1 Adverse Event (AE) Start (Onset) Date and Stop Date Imputation

AE start (onset) date and stop date are separated into 3 different data fields, including day, month and year. Completely missing AE date (ie, missing day, missing month and missing year) will not be imputed. Partial AE start date will be imputed according to the rules as follows in a sequential fashion.

In the imputation of missing or partial dates, if the imputed date is after min (death date, cutoff date), min (death date, cutoff date) will be used as the imputed date.

AE Stop Date

- If month and year are present, then impute as the last day of that month
- If only the year is present, impute as December 31 of that year
- If the stop date is entirely missing, assume the event is ongoing

AE Start Date

- If month and year are present, and are not equal to the month and year of the first dose, then imputed as the first day of the month
- If month and year are present, and are equal to the month and year of first dose
    - If stop date is complete and earlier than the date of first dose, then impute as the first day of the month
    - Else impute as the date of first dose
- If only the year is present, and the year is not equal to the year of the first dose, then impute as January 1 of the year
- If only the year is present, and the year is equal to the year of the first dose
    - If stop date is complete and earlier than the date of first dose, then impute as January 1 of the year
    - If stop date is partially missing and the month and year of stop date are earlier than the month and year of first dose, then impute as January 1 of the year
    - Else impute as the date of first dose

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- If the start date is entirely missing
  - If the stop date is complete and earlier than the date of first dose, then impute as January 1 of the stop year
  - If the day of stop date is missing, and the month and year are earlier than the month and year of first dose, then impute as January 1 of the stop year
  - If the day and month of stop date are missing, and the year is earlier than the year of first dose, then impute as January 1 of the stop year
  - Else impute as the date of first dose

8.1.2 Concomitant Medication (CM) Start Date and Stop Date Imputation

The imputation rules for CM are the same as the rules for AE.

8.1.3 Other Date Imputations

In the case of partial start date of post treatment systemic anti-cancer therapy, the date will be imputed as the first day of the month but not earlier than the last dose date. A month and year must be present or the date will remain missing.

8.2 Criteria for Abnormal Values for Vital Signs

Table 5 Criteria for Abnormal Vital Sign Values

Vital Signs Parameter	Low	High
Pulse rate (bpm)	<45	>130
Systolic blood pressure (mmHg)	<80	>155
Diastolic blood pressure (mmHg)		>100
Respiratory Rate (breaths per minute)		> 25
Temperature (◦C)	≤ 35	≥ 38
Source: *FDA Guidance for Industry 2007, Toxicity Grading Scale for Health Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials*		

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