20 July 2023
EMA/CHMP/358130/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Orserdu

International non-proprietary name: elacestrant

Procedure No. EMEA/H/C/005898/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

Abbreviation	Definition
ADME	Absorption, distribution, metabolism, and excretion
ADME/PK	Absorption, distribution, metabolism, excretion, and pharmacokinetics
ADRA2A	Adrenergic receptor alpha 2a
AI	Aromatase inhibitor
AUC	Area under the concentration-time curve
AUC0-24	Area under the plasma concentration-time curve from time zero to 24 hours postdose
BOR	Best overall response
C1D1… CxDx	Cycle 1 Day 1… Cycle x Day x
CBE	Clinical-Benefit-Evaluable
CBR	Clinical benefit rate
CDK4/6	Cyclin-dependent kinase 4/6
CDK4/6	Cyclin-dependent kinase 4/6
CDX	Cell line-derived xenograft
CI	Confidence interval
Cmax	Maximum plasma concentration
CMC-Na	Carboxymethylcellulose sodium salt
CNR	Cannabinoid receptor
CNS	Central nervous system
CQA	Critical quality attribute
CR	Complete response
ctDNA	Circulating tumour deoxyribonucleic acid
CYP	Cytochrome P450
DCO	Data cutoff
DoR	Duration of response
E2	Oestradiol
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	EuroQol 5 Dimension 5 Level
EQ-VAS	EuroQol visual analogue scale
ER	Oestrogen receptor
ER+	Oestrogen receptor positive
ERα	Oestrogen receptor-alpha
ERβ	Oestrogen receptor-beta
ESMO	European Society of Medical Oncology
ESR1	Oestrogen receptor 1
ESR1	Oestrogen receptor gene 1
ESR1-mut	*ESR1* mutation positive
ESR1-mut-nd	No *ESR1* mutations detected (includes samples where *ESR1* mutations were not present, e.g., wild type, or samples with *ESR1* mutations outside biomarker definition)
FDA	Food and Drug Administration
FES-PET	Fluoroestradiol-positron emission tomography
FTIR	Fourrier Transform Infrared Spectroscopy
GLP	Good laboratory practice

HER2	Human epidermal growth factor receptor 2
HER2-	Human epidermal growth factor receptor 2 negative
hERG	Human ether-à-go-go-related gene
HPLC	High performance liquid chromatography
HR	Hazard ratio
HRQOL	Health-related quality of life
IC50	Half-maximal inhibitory concentration
ICH	International Conference on Harmonisation
ICP-MS	Inductively coupled plasma mass spectrometry
IDMC	Independent Data Monitoring Committee
IM	Intramuscular(ly)
IPC	In-process control
IR	Infrared
IRC	Imaging Review Committee
ITT	Intention-to-Treat
IV	Intravenous
KM	Kaplan-Meier
LH	Luteinizing hormone
MATE	Multidrug and toxin extrusion
mBC	Metastatic breast cancer
MMRM	Mixed model repeated measures
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NE	Not evaluable
NOAEL	No observed adverse effect level
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
ORR	Objective response rate
OS	Overall survival
PAR	Proven acceptable range
PD	Progressive disease
PDX	Patient-derived xenograft
PFS	Progression-free survival
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic(s)
PP	Per-protocol
PR	Partial response
PRO	Patient-reported outcome
PRO-CTCAE	Patient-reported outcome-common terminology criteria for adverse events
Q1	First quartile
Q3	Third quartile
QbD	Quality by design
QD	Once daily
QLQ-C30	Quality of Life Questionnaire-Core 30
QTPP	Quality target product profile
RE	Response-evaluable

RECIST	Response evaluation criteria in solid tumours
RP2D	Recommended phase 2 dose
S-1901	S-enantiomer of elacestrant
SAP	Statistical analysis plan
SCE	Summary of clinical efficacy
SD	Stable disease
SERD	Selective oestrogen receptor degrader
SERM	Selective oestrogen receptor modulator
SOC	Standard of care
TGI	Tumour growth inhibition
TK	Toxicokinetic(s)
USP/NF	United States Pharmacopoeia/National Formulary
USPI	United States Prescribing Information
UV	Ultraviolet
XPRD	X-Ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Stemline Therapeutics B.V. submitted on 27 July 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Orserdu, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 March 2021.

The applicant applied for the following indication: Orserdu is indicated for the treatment of postmenopausal woman, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced or metastatic breast cancer who have progressed following at least one line of endocrine therapy.

1.2. Legal basis and dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/0001/2015 on the granting of a class waiver as elacestrant, proposed for the indication "treatment of advanced/metastatic ER+ breast cancer" is considered to belong to the class of oestrogen receptor modulator medicinal products for treatment of breast malignant neoplasms.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. New active Substance status

The applicant requested the active substance elacestrant contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. PRIME

Not applicable

1.7. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
22 February 2018	EMEA/H/SA/3753/1/2018/SME/III	Martin Mengel, Brigitte Blöchl-Daum

The scientific advice pertained to the following non-clinical and clinical aspects:

- Adequacy of the proposed nonclinical data package to support a marketing authorisation application.
- Adequacy of the proposed dose
- Design of the proposed single-arm phase II Study RAD1901-108, in particular with regards to the choice of patient population (women with ER+ / HER2- advanced or metastatic breast cancer who have relapsed or progressed following 2 prior lines of hormonal therapy, which must have included fulvestrant and a CDK4/6i, and up to 1 line of prior chemotherapy) and study endpoints and its adequacy to support a marketing authorisation application.

1.8. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Janet Koenig

CHMP Peer reviewer(s): N/A

The application was received by the EMA on	27 July 2022
The procedure started on	18 August 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	7 November 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	21 November 2022
The CHMP Co-Rapporteur's first Assessment Report / Critique was circulated to all CHMP and PRAC members on	21 November 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	15 December 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	20 March 2023

The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	03 May 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 May 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	25 May 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	17 June 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	5 July 2023
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Orserdu on	20 July 2023
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	20 July 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Claimed therapeutic indication:

Orserdu is indicated for the treatment of postmenopausal woman, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced or metastatic breast cancer who have progressed following at least one line of endocrine therapy.

2.1.2. Epidemiology and risk factors

Breast cancer (BC) is the leading cause of cancer in women and the leading cause of cancer deaths in women (Bray et al, *CA*: *A Cancer Journal for Clinicians,* 2018). The incidence and prevalence of patients with invasive breast cancer, as well as estimates for the prevalence of subjects with ER+/HER2- breast cancer, are presented in Table 1.

Table 1 Epidemiology of ER+/HER2- Breast cancer (x 1,000)

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

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

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

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

For women diagnosed with early BC (EBC), the 5-year survival probability is ~96% in Europe. However, when metastatic BC (MBC) is diagnosed, the 5-year survival rate is in the range of 38% (Allemani et al, *Lancet*, 2018). About 157,100 women were estimated to have died from breast cancer in the EU in 2020 (Ferlay et al, *International Journal of Cancer*, 2021). In terms of absolute numbers, MBC was still the leading cause of death from all cancers in women, accounting for ~3.6% of all deaths in women and 1.8% of all deaths in Europe in 2015 (Dafni et al, *Breast Care*, 2019).

2.1.3. Biologic features, aetiology and pathogenesis

BC is a heterogeneous disease comprising different subtypes, which can be identified through molecular biomarkers that also act as predictive factors. It is categorised into different histopathologic subtypes based on the expression of the oestrogen receptor (ER), the progesterone receptor (PR), and HER2 receptor overexpression or gene amplification[1]. Of the new cancers diagnosed worldwide each year, about 70%-80% are hormone receptor (HR)-positive (Joe et al, *UpToDate*, 2021).

ER is a transcription factor that regulates the expression of oestrogen-responsive genes by binding to a specific DNA sequence found in their regulatory regions. Two major isoforms of the oestrogen receptor have been identified, ERα and ERβ: however, the role of ERβ in cancer remains unclear. The two isoforms are encoded by two genes located on different chromosomes (ESR1 on chromosome 6 and ESR2 on chromosome 14) and regulate different specific genes. Recent ASCO/College of American Pathologists guidelines still support the classification of ER+ breast cancer being > 1% by immunohistochemistry staining. Similar principles apply to PR testing, which is used primarily for prognostic purposes in the setting of an ER-positive cancer. HR+/HER2− breast cancer is characterized by hormone receptor positivity (> 1% IHC expression of the oestrogen receptor [ER] and/or progesterone receptor) and lack of HER2 expression (IHC score of 0, 1+, or 2+ confirmed as negative by in situ hybridization [ISH]) (Allison et al., 2020, Wolff et al., 2018). Other therapeutically relevant biomarkers to be assessed include phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) in ER/PR-positive, HER2-negative MBC.

Endocrine therapy (ET) comprises different strategies as suppression of oestrogen production or directly targeting the oestrogen receptor (ER). Steroidal/nonsteroidal aromatase inhibitors (AI, exemestane/letrozole and anastrozole and exemestane) exert their action by blocking androgen to oestrogen conversion, thus lowering the levels of circulating oestradiol (E2) and, therefore, reducing the activation of ER. Direct targeting of ERα is achieved by selective oestrogen receptor modulator (SERM) (e.g., tamoxifen) and selective oestrogen receptor degrader (SERD) (e.g., fulvestrant). SERMs compete with oestrogen for ER binding and show mixed agonist/antagonist capabilities in a tissue-specific fashion. Meanwhile, SERDs create an unstable protein complex that induces ER protein degradation via the proteasome.

Several mechanisms regarding ER have been considered to drive resistance to anticancer drugs. Within these, alterations in ESR1 are some of the most well-established and the main subject of interest to this date. *ESR1* mutations are characteristically more frequent in advanced disease, after endocrine therapy and mostly AI, rather than in primary BC. Mutations in *ESR1* are found in the ligand-binding domain (LBD), favouring constitutive ER activation independent from oestrogen and resistance to AIs. However, *ESR1* mutated tumours can still present sensitivity to tamoxifen or fulvestrant. Mutations in Y537S and D538G are the most frequently described mutations. All *ESR1* LBD mutations cause complete AI resistance; however, preclinical studies indicate Y537S has the highest transactivation activity and the greatest relative resistance to tamoxifen, fulvestrant, and some of the novel SERDs and SERMs. In addition, Y537S-specific *ESR1* mutations are reported as drivers of resistance to fulvestrant plus palbociclib combination therapy (O'Leary et al, *Cancer Discovery*, 2018; Dustin et al, *Cancer*, 2019; Hernando et al, *International Journal of Molecular Sciences*, 2021; Jeselsohn et al, *Nature Reviews Clinical Oncology*, 2015).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

The diagnosis of breast cancer is based on clinical examination in combination with imaging and confirmed by pathological assessment. Disease stage is assessed according to the Tumour, Node, Metastasis (TNM) system.

A number of previous studies on patients with MBC have demonstrated that compared with wild-type *ESR1*, *ESR1* mutation led to worse progression-free survival (PFS) and overall survival (OS) (Chandarlapaty et al, *Oncotarget*, 2016).

2.1.5. Management

The aim of treatment is to increase PFS and OS. Key clinical factors to consider when determining the choice for systemic treatment for women are (1) pre- versus postmenopausal status at the time of presentation, (2) de novo metastatic versus recurrence, (3) disease-free interval and type of adjuvant therapy, (4) tumour burden including bone-only versus visceral disease, (5) performance status and medical comorbidities, and (6) for patients who have progressed on frontline treatment to consider the previous treatments they received and the response, duration of response, and tolerability to those previous therapies (Andrew et al, JCO Oncology Practice, 2021).

The current first-line standard of care (SOC) for locally advanced or metastatic ER+/HER2- breast cancer is endocrine therapy, with either aromatase inhibitors or fulvestrant, plus a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor (palbociclib, ribociclib, abemaciclib).

The optimal sequence of endocrine-based therapy is uncertain after progression on CDK4/6 inhibitors and limited data is available post-CDK4/6 inhibitor treatment.

Treatment guidelines, when the pivotal (RAD1901-308) trial was initiated in 2018 and still currently, recommend the use of sequential endocrine therapy in the absence of visceral crisis until all endocrine therapy options have been exhausted (NCCN, 2018; NCCN, 2022; Gennari et al, *Annals of Oncology*, 2021). Endocrine therapy includes endocrine monotherapy, such as fulvestrant or aromatase inhibitors, depending on the first-line therapy applied (NCCN, 2021; Burnstein et al, *Journal of Clinical Oncology*, 2021; Gennari et al, *Annals of Oncology*, 2021). Available 2nd line combination therapy options are everolimus + exemestane (median PFS 7.8 months) (BOLERO-2; Yardley et al., 2013) and everolimus +fulvestrant/tamoxifen.

For subjects with *PIK3CA*-mutant breast cancer, the combination of fulvestrant and alpelisib is another option (median PFS 11.0 month and median OS 39.3 months), (Andre et al., 2020). PARP inhibitor monotherapy (olaparib or talazoparib) have been proposed to be considered for patients with germline pathogenic BRCA1/2 mutations and as an option for those with somatic pathogenic or likely pathogenic BRCA1/2 or germline PALB2 mutations (Gennari et al, *Annals of Oncology*, 2021). Overall, ESMO guideline recommends using at least two lines of endocrine-based therapy before moving to chemotherapy. In patients with high disease burden and upcoming organ failure, chemotherapy is a preferred option.

To overcome the issues of an intramuscular administration route, several oral SERDs, besides elacestrant, are in development investigating both monotherapy and combination with CDK4/6 inhibitors (Downton et al, Drug Design, *Development and Therapy*, 2022). At ESMO 2022, mixed results were presented for two of these SERDs in advanced BC.

2.2. About the product

Elacestrant, a tetrahydronaphthalene compound, is a potent, selective and orally active oestrogen receptor-α (ERα) antagonist and degrader. Elacestrant inhibits the oestradiol-dependent and independent growth of ERα-positive breast cancer cells, including models harbouring oestrogen receptor 1 (*ESR1*) gene mutations. Elacestrant displayed potent antitumour activity in patient derived xenograft models previously exposed to multiple endocrine therapies, harbouring wild type *ESR1* or *ESR1* gene mutations in the ligand binding domain. (See SmPC section 5.1).

The claimed indication for Orserdu was: Orserdu monotherapy is indicated for the treatment of postmenopausal woman, and men, with oestrogen receptor (ER)-positive, human epidermal growth

factor receptor 2 (HER2)-negative, advanced or metastatic breast cancer with an ESR1 mutation who have progressed following at least one line of endocrine therapy.

Following recommendation by the CHMP the applicant agreed to a revised indication wording: Orserdu monotherapy is indicated for the treatment of postmenopausal women, and men, with oestrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK4/6 inhibitor. (See SmPC section 4.1).

Treatment with ORSERDU should be initiated by a physician experienced in the use of anticancer therapies.

Patients with ER-positive, HER2-negative advanced breast cancer should be selected for treatment with ORSERDU based on the presence of an activating ESR1 mutation in plasma specimens, using a CE marked *in vitro* diagnostic (IVD) with the corresponding intended purpose. If the CE-marked IVD is not available, the presence of an activating ESR1 mutation in plasma specimens should be assessed by an alternative validated test.

The recommended dosage is 345 mg (one 345 mg film-coated tablet) taken orally, once daily, with food. The maximum recommended daily dose of ORSERDU is 345 mg. A dose reduction is allowed in case of adverse reactions to 258 mg once daily. (See SmPC section 4.2 and see 2.6.9.). If further dose reduction below 258 mg once daily is required, the treatment should be discontinued.

Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs. (See SmPC section 4.2). If a dose is missed, it can be taken immediately within 6 hours after the time it is usually taken. After more than 6 hours, the dose should be skipped for that day. On the next day, ORSERDU should be taken at the usual time.

2.3. Type of application and aspects on development

Several PK studies have been performed in healthy men and postmenopausal women and in postmenopausal women and men with mBC. Initially, a single-arm phase 2 study with ORR as primary endpoint, was proposed at Scientific Advice, as the single pivotal study for future MAA in the proposed target population. The CHMP did not agree that this single arm study would define clinical benefit and a positive B/R in the absence of an active comparator given established treatment options. Based on the SA, the applicant revised their intended clinical strategy. The clinical development programme in support of the proposed indication concerns three clinical studies; 2 phase 1 studies in postmenopausal women with pretreated ER+/HER2-advanced or mBC (Rad1901-005 and RAD1901-106) in support of the recommended dose of 400 mg QD and one phase 3 RCT (RAD1901-308) in the proposed indication.

The study considered to be key to the proposed indication is study RAD1901-308 (hereafter referred to as study 308), a phase 3 randomized, open-label study comparing elacestrant versus standard of care (SOC, fulvestrant or aromatase inhibitor (AI)) in postmenopausal women and men with advanced or metastatic ER+/HER2-breast cancer.

Of note, at scientific advice, the applicant was encouraged to study PK in patients with impaired renal GFR below 60 ml/min) and hepatic function (mild ALT, AST and bilirubin elevation), as this would need to be addressed at the time of an MAA.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film-coated tablet containing 86 mg or 345 mg of elacestrant (as dihydrochloride) as active substance.

Other ingredients are:

Tablet core: microcrystalline cellulose [E460], silicified microcrystalline cellulose, crospovidone [E1202], magnesium stearate [E470b], colloidal silicon dioxide [E551]

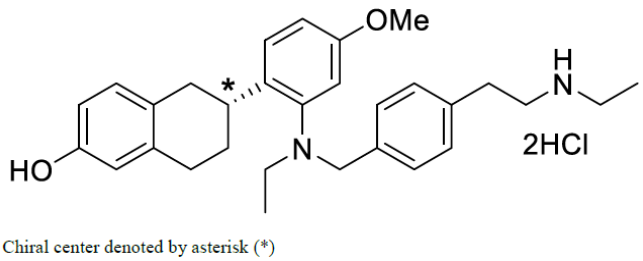
Film-coating: Opadry II 85F105080 Blue (polyvinyl alcohol [E1203], titanium dioxide [E171], macrogol [E1521], talc [E553b] and Brilliant Blue FCF Aluminum Lake [E133])

The product is available in alu-alu blisters as described in section 6.5 of the SmPC.

2.4.2. Active substance: elacestrant dihydrochloride

General information

The chemical name of elacestrant dihydrochloride is ((6R)-6-(2-(N-(4-(2-(ethylamino)ethyl)benzyl)-N-ethylamino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol dihydrochloride) corresponding to the molecular formula $C_{30}H_{38}N_2O_2$ (· 2HCl). It has a relative molecular mass of 531.56 and the following structure:



Chiral center denoted by asterisk (*)

Figure 1: Elacestrant dihydrochloride structure

The chemical structure of elacestrant dihydrochloride was elucidated by a combination of infrared spectroscopy (IR), proton nuclear magnetic resonance (^{1}H NMR), carbon nuclear magnetic resonance (^{13}C NMR), low-resolution mass spectrometry (MS), UV spectroscopy, elemental analysis and single-crystal X-ray crystallography. The solid state properties of the active substance were measured by X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC) and optical rotation.

Elacestrant dihydrochloride is a white to off-white to grey solid soluble in acidic aqueous medium, forms a suspension in most organic solvents and it is non-hygroscopic.

Elacestrant dihydrochloride exhibits stereoisomerism due to the presence of one chiral centres. The proposed active substance has the R-absolute configuration. Enantiomeric purity is controlled routinely. Polymorphism has been observed for elacestrant dihydrochloride.

Manufacture, characterisation and process controls

Elacestrant dihydrochloride is synthesized in seven main steps using well defined starting materials with acceptable specifications. The manufacturing process has been developed using a combination of conventional univariate studies and elements of QbD such as risk assessment. The critical quality attributes (CQAs) were identified.

A risk analysis was performed in order to define critical process steps and process parameters that may have an influence on the on the active substance CQAs. Proven acceptable ranges (PARs) have been defined for the manufacture of the active substance. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs. Adequate in-process controls are applied during the synthesis.

The specifications and control methods for intermediate products, starting materials and reagents have been presented, updated during the procedure and they are now considered acceptable.

The synthetic route to elacestrant dihydrochloride was developed by one manufacturer and optimised by the manufacturer proposed for marketing. A comparability of batch analysis data demonstrates that the final active substance is comparable across the processes. Changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development programme.

The active substance is packaged in double LDPE bags which complies with Commission Regulation (EU) 10/2011, as amended.

Specification

The active substance specification includes tests for: appearance (visual examination), identification (FTIR, HPLC and XPRD for the polymorphic form), assay (anhydrous and dry basis, by HPLC), organic impurities (HPLC), S-Enantiomer (HPLC), water content (Ph. Eur.), Residue on ignition (Ph. Eur. 2.4.14), Particle size distribution (Laser light scattering), chloride content (ion chromatography), acetic acid content (HPLC), residual solvents (gas chromatography), elemental impurities (ICP-MS) and microbiological evaluation (Ph. Eur.).

Although batch data for 'assay on anhydrous basis' would support a tighter limit than the proposed one, in view of the limited amount of produced batches up to now, it can be accepted as the additional parameter 'assay on dried basis' has been added to the specification.

Based on batch data, the following limits have been lowered: total impurities, S-enantiomer, chloride content, water content and boron.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

With regard to potentially genotoxic impurities, although elacestrant dihydrochloride is intended for an advanced cancer indication and falls under the scope of ICH S9, ICH M7 has been considered and a toxicological assessment has been performed in silico for all impurities. Two impurities have been identified as potentially genotoxic and are adequately controlled.

All residual solvents used in the active substance manufacturing process are listed in the active substance specification have been tested in eight registration batches. Since several solvents may contain Class 1 solvents, their absence has been shown on three consecutive industrial scale batches of the active substance or intermediate. Genotoxicity of solvents and reagents has also been adequately addressed.

The inorganic impurities and the elemental impurities are adequately controlled in the final active substance.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data three full-scale commercial batches of the active substance, manufactured by the proposed finished product manufacturer, together with eighth pilot manufactured by the proposed finished product manufacturer and 8 pilot batches manufactured by the previous manufacturer and used during the clinical trials are provided. The results are within the specifications and consistent from batch to batch.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Stability

Stability data from 8 pilot scale batches (>10% of the commercial batch scale) of active substance from the proposed manufacturer stored in the intended commercial package for up to 18 months under long term (25ºC / 60% RH) and intermediate conditions (30ºC / 75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The parameters tested are appearance, polymorphic identity, assay, drug related impurities, chiral purity, water content and microbial quality attributes, in line with the methods indicated in the Specification section. Photostability testing following the ICH guideline Q1B was performed on samples of the active substance. Samples of the active substance were also subjected to stress conditions of 50°C for up to 1 week. All tested parameters were within the specifications.

The analytical methods used were the same as for release and were stability.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months without special storage conditions in the proposed container.

2.4.3. Finished medicinal product

Description of the product and pharmaceutical development

The finished product is presented as film-coated tablet containing 86 mg or 345 mg of elacestrant (as dihydrochloride) as active substance.

Each Orserdu 86 mg film-coated tablet contains elacestrant dihydrochloride equivalent to elacestrant 86.3 mg; the tablets are blue to light blue biconvex round shaped film-coated tablet with ME debossed on one side and plain face on the opposite side. Approximate diameter: 8.8 mm.

Each Orserdu 345 mg film-coated tablet contains elacestrant dihydrochloride equivalent to elacestrant 345 mg; the tablets are blue to light blue biconvex oval shaped film-coated tablet with MH debossed on one side and plain face on the opposite side. Approximate size: 9.2 mm (length), 10.8 mm (width).

The qualitative composition of the finished product is given in Table 2; the qualitative composition of silicified microcrystalline cellulose and of Opadry II 85F105080 Blue are given in Table 3 and Table 4 respectively.

Table 2: Composition of finished product

Excipient	Grade
Tablet Core	
Elacestrant Dihydrochloride	In-house
Microcrystalline Cellulose [E460]	NF/Ph.Eur.
Silicified Microcrystalline Cellulose	NF
Crospovidone [E1202]	USP/NF/Ph.Eur.
Magnesium Stearate (non-bovine) [E470b]	USP/NF/Ph.Eur./JP
Colloidal Silicon Dioxide [E551]	USP/NF/Ph.Eur./JP
Film-Coating	
Opadry II 85F105080 Blue	Non-Compendial
Purified Water[a]	USP/Ph.Eur.

[a] Removed during processing.

Table 3: Composition of silicified microcrystalline cellulose

Component	Quality reference
Microcrystalline cellulose [E460]	NF/Ph. Eur./JP
Colloidal silicon dioxide [E551]	NF/Ph. Eur./JP

Table 4: Composition of Opadry II 85F105080 Blue

Component	Quality Reference
Polyvinyl Alcohol [E1203]	USP/FCC/Ph.Eur./JPE
Titanium Dioxide [E171]	USP/Ph.Eur./FCC/JP/ChP/GB
Macrogol [E1521]	USP/FCC/Ph.Eur./JECFA/JP
Talc [E553b]	USP/FCC/Ph.Eur./JECFA/JP
FD&C Blue #1/Brillant Blue FCF Aluminum Lake [E133]	JECFA/JP MO/GB

The solubility of active substance at various pH has been properly investigated and discussed. All excipients are well-known pharmaceutical ingredients and their quality, or the quality of their individual components, for microcrystalline cellulose (NF) and Opadry coating (in-house), is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. Compatibility of drug substance and excipients has been shown.

It has been shown that storage of the active substance and manufacturing / storage of the finished product do not affect the polymorphic form and that there is no relevant change in stereochemistry. The impact of active substance particle size on dissolution has been adequately investigated.

Pharmaceutical development of the finished product contains QbD elements. The quality target product profile is summarised in Table 5 below.

Table 5: QTPP of the finished product

Product Attribute	Target	Outcome for Elacestrant tablets, 100 mg and 400 mg
Route of administration & dosage form	Immediate release solid oral dosage form	There are no orally delivered SERDs on the market. The only approved SERD is fulvestrant which requires intramuscular administration. Elacestrant is an immediate release tablet, dose-weight proportional for the two strengths.
Dose range and frequency	As required by clinical trials	Max dose 400 mg/once daily
Pharmacokinetics	Orally bioavailable with maximum plasma concentrations achieved within hours after dosing of immediate release drug product formulation (similar PK profile achieved for both dose strengths)	Complies with target
Shelf Life	Minimum of 24 months at long-term storage conditions	Complies with target
Requirement to assure safety and efficacy at release and during shelf-life	All appropriate quality criteria are met (for appearance, identification, assay, content uniformity, dissolution, impurities, water content, and microbial content).	Complies with target

SERD = Selective Estrogen Receptor Degrader

The critical quality attributes identified were: appearance, identification, assay, related substances, uniformity of dosage units, dissolution, water content, microbial limits. The formulation and manufacturing development have been evaluated through the use of risk assessment and design of experiments to identify the critical product quality attributes and critical process parameters. A risk

analysis was performed using the failure mode effect analysis (FMEA) method in order to define excipients levels, critical process steps and process parameters that may have an influence on the finished product quality attributes. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development, process design and scale-up studies. Appropriate blend uniformity as well as ranges for critical excipients and process parameters for granulation and compression has also been shown. The critical process parameters for blending, roller compaction and compression unit operations have been adequately identified.

An immediate release (IR) film-coated tablet formulation of elacestrant dihydrochloride was developed and used for clinical trials. The manufacturing method consists of manufacture of common blend, compression, coating and packaging. The roller compaction in the final blend process is designed to enhance blend flowability while maintaining its compatibility for high-speed tablet compression. Subsequently, the formulation was optimised for producing large scale registration and commercial batches, however the manufacturing process and unit operations remained the same as for all clinical batches.

Acceptability of the formulation and packaging for the older population is discussed in line with the reflection paper. Enteral feeding tubes administration is not foreseen. An open dish study was performed to support the stability of the product when stored in caddies.

Storage of bulk product (film-coated tablets) is proposed for 12 months at 15° - 25°C, which is sufficiently supported by data.

The development of QC dissolution method has been described in detail. Dissolution medium, volume and stirrer speed were discussed and justified. The discriminatory power of the chosen QC dissolution method has been demonstrated; in fact, the method is over discriminatory when compared to *in vivo* data.

The primary packaging is alu - alu blisters. The material complies with Ph.Eur. and EU regulations 10/2011. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of four main steps: manufacture of common blend (pre-compaction blending, roller compaction, and final blending), compression (tableting), coating and packaging. The process is considered to be a standard manufacturing process.

Roller compaction and compression have been identified as critical steps. Both are appropriately controlled. Process parameter ranges are in line with the control strategy based on manufacturing process development.

Bulk product (film-coated tablets) may be stored for up to 12 months. Storage conditions and description on bulk product packaging are presented. Major steps of the manufacturing process have been validated by a number of studies.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls have been justified and reviewed during the procedure; they are now considered as adequate for this type of manufacturing process.

A process validation protocol has been submitted and validation will be performed prior to marketing of batches. Taking into account the extensive development data presented and that the finished product is manufactured according to a standard process, this approach is considered adequate.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual examination), identification (UV and HPLC), assay and related substances (HPLC), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur., HPLC), water content (Ph. Eur.), microbial limits (Ph. Eur.) and specified microorganisms.

Release and shelf-life specification have been provided and meet Ph. Eur. and guidance requirements. The specification limits are based on applicable regulatory guidance and batch data, including clinical batch data. The specifications are now considered satisfactory.

One specified impurity was identified; it is a potential degradation product arising from the oxidation of the active substance.

Since polymorphic form and chiral purity/S-enantiomer content do not change during the manufacture and storage of the finished product, and are controlled at the level of the active substance, the absence of these tests form the finished product specification is accepted.

Except for water, no organic solvents are used in the manufacture of elacestrant tablets. The residual solvent content of active substance is controlled at release. A risk assessment was conducted on the potential residual solvents content in the finished product by evaluating the manufacture process and the potential residual solvents present in all excipients. Both strengths of the drug product meet the ICH Q3C requirements. Therefore, no residual solvent testing is required.

The dissolution limit for both strengths has been justified and is considered acceptable.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on three batches using a validated ICP-MS method were provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data, it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided and considering that the finished product falls in the scope of ICH S9, and hence nitrosamines should be controlled in line with ICH Q3B, it is accepted that the risk of nitrosamine impurities in the active substance or the related finished product is negligeable. Therefore, no specific control measures are deemed necessary.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three full-scale batches of each strength, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three full-scale batches of each strength of finished product stored for up to 9 months under long term (25ºC / 60% RH) and intermediate (30ºC / 75% RH) conditions for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of finished product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Supportive stability data from three full-scale batches of each strength of finished product stored for up to 12 months under long term (25ºC / 60% RH) and intermediate (30ºC / 75% RH) conditions for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of finished product are representative to those proposed for marketing and were packed in in HDPE bottles, which can be considered worst case compared to alu-alu blisters.

Samples were tested for appearance, dissolution, water content, assay, related substances and microbial limits in line with the shelf-life specifications. All results comply with the corresponding limits and no relevant trend is observed at any tested condition. The analytical procedures used were demonstrated to be stability indicating during validation.

In addition, one full-scale batch per strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The data confirm that the unpacked finished product is stable to light.

Based on available stability data, the proposed shelf-life of 2 years without specific storage conditions, as stated in the SmPC (sections 6.3 and 6.4), are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

All pivotal non-clinical studies relevant for the non-clinical safety assessment of elacestrant (safety pharmacology studies to assess the cardiovascular system *in vitro* and *in vivo* (in cynomolgus monkeys), central nervous system and respiratory function in rats, pivotal repeat-dose toxicity studies, genotoxicity studies, embryo-foetal development in rats, local tolerance, and *in vitro* phototoxicity) were conducted in compliance with Good Laboratory Practice (GLP) principles.

2.5.2. Pharmacology

In vitro studies were conducted to evaluate the binding affinity of elacestrant for ERα, the antagonism of the effects induced by oestradiol (E2), and the ability of elacestrant to down-regulate and degrade ERα. The *in vitro* antiproliferative activity of elacestrant against several ER-positive breast cancer cell lines and the antitumour activity of elacestrant in breast cancer xenograft mouse models were evaluated. These studies included the use of breast cancer cells, insensitive to fulvestrant and CDK4/6 inhibitors, and of cells harbouring mutations in ESR1. The enantiomer S-1901 was used as a comparator in several of the *in vitro* studies, and fulvestrant was used as a comparator in the xenograft models because it is currently the only drug endowed with SERD properties approved for the treatment of ER-positive advanced breast cancer. Additionally, elacestrant antitumour activity was compared with selective ER modulators, CDK4/6 inhibitors, a mammalian target of rapamycin inhibitor, and a phosphoinositide 3-kinase inhibitor.

The potential off-target activity of elacestrant was evaluated against a panel of 166 molecular targets and further in cell-based assays for activity at cannabinoid receptor type 1 and 2 (CNR1 and CNR2, respectively) and adrenergic receptor α2a (ADRA2A). Additional secondary pharmacology studies investigated the uterotrophic effects of elacestrant in immature mice and rats, the ability of elacestrant to regulate luteinizing hormone (LH) release and prevent bone loss in ovariectomized rat models, and the efficacy of elacestrant in a rat model of vasomotor instability.

In vitro and *in vivo* safety pharmacology studies were performed to assess cardiac, respiratory, and neurological effects of elacestrant. Other safety pharmacology studies investigated the effects of elacestrant on bleeding time, wound healing, and the gastrointestinal system.

2.5.2.1. Primary pharmacodynamic studies

Elacestrant as an oestrogen receptor binder

The binding modality of elacestrant to ERα was resolved by X-ray crystallography and showed a unique pattern of interaction as compared to other compounds of the same pharmacological class. Elacestrant maintained hydrophobic interactions in the core and took a vector close to the H11 and the H11-12 loop. The H12 conformation governs agonist and antagonist activities, and molecules that perturb the H11-12 loop or H12 directly have selective oestrogen receptor degrader (SERD) activity. When compared to the binding of other SERDs and selective oestrogen receptor modulators (SERMs), elacestrant displayed a particular pattern of molecular interactions with the WT ERα ligand binding domain (LBD) (Chinnasamy et al 2020, Report 19RAD221).

Elacestrant as an oestrogen receptor antagonist

Elacestrant (RAD-1901) bound with high affinity to ERα with an IC50 of 48 nM and S-1901 bound with lower affinity for ERα with an IC50 of 108 nM. The E2 control had an IC50 of 0.4 nM. Both Elacestrant and S-1901 also bound to ERβ, although with lower affinity (IC50 of 870 and 940 nM, respectively) than to ERα. This study showed that elacestrant was a selective ligand for ERα. Elacestrant itself (1pM-10uM) did not stimulate proliferation of MCF-7 cells. Co-treatment of these cells with both elacestrant and E2 resulted in a concentration-dependent decrease of E2-induced proliferation of MCF-7 cells, with IC50 values for elacestrant of 4.2 nM (E2 concentration at 0.01 nM) and 27 nM (E2 concentration at 0.1 nM), respectively. S-1901 possesses the same qualities albeit at higher IC50. In SKBR3 cells transiently transfected with human ERα and ERβ, elacestrant effectively inhibits E2-dependent activation of an oestrogen response element (ERE)-luciferase reporter by either isoform, being a more potent inhibitor of ERα than of ERβ (100-fold), displaying nanomolar potency. Data from these studies showed that elacestrant was a potent ER antagonist (Studies Rad-001, Rad-002 and Wardell et al 2015a).

Elacestrant as an oestrogen receptor degrader

The decrease in ERα protein levels following elacestrant treatment in MCF-7 cell lines was further showed in a study by Wardell et al 2015a. Based on this study, treatment of MCF-7 cells with elacestrant (10 pM to 10 μM) for 24 hours produced a concentration-dependent decrease of ERα protein, with effects observed in the low nanomolar range. Furthermore, the addition of proteasome inhibitor MG132 restored the ERα protein to levels comparable to that in vehicle-treated MCF-7 cells, suggesting that elacestrant-induced decrease in ERα protein was proteasome ubiquitin-mediated. In a Duo Set ERα assay, elacestrant produced a concentration-dependent reduction in ERα protein levels in MCF-7 and T47D (luminal A subtype) cell lines with an EC50 (normalized to DMSO treatment) for elacestrant of 0.6 nM in MCF-7 cells and 76 nM in T47D cells (test range of 0.5 nM to 10 μM, 48 hours). In contrast to MCF-7 and T47D, ERα protein level was slightly increased in the BT474 (luminal B subtype) cell line (140% at 10 μM) treated with elacestrant, which could be related to the high level of ER-c-Src-HER2 complex formation in this cell line, which hinders the binding of the compound to the LBD of ERα.

When MCF-7 cells were incubated with elacestrant (10 pM to 10 μM) for 24 hours, this resulted in a concentration-dependent decrease of ERα protein (effects observed already at low nanomolar range), which was counteracted by incubation with proteasome inhibitor MG132. These data suggest that elacestrant-induced decrease in ERα protein was proteasome ubiquitin-mediated.

In addition, treatment of MCF-7, T47D, and also HCC1428 cells with elacestrant (1 nM to 1 μM for 48 hours) led to a reduction in ER protein levels (evaluated through Western blotting) in a concentration-dependent manner. However, ER levels were lower upon fulvestrant incubation compared to elacestrant binding suggesting that fulvestrant is about 10- to 100-fold more effective at ER degradation. The IC50 of fulvestrant for growth inhibition in MCF-7 was 0.8 nM. This was lower than the IC50 of elacestrant for growth inhibition in MCF-7. The latter was 4.2 nM with and 5.6 nM without E2, respectively, suggesting that the potency of elacestrant was 10-fold lower than potency of fulvestrant (Nukatsuka et al, 2019) (Reports STC-RAD-02, 16RAD203, 16RAD209, 16RAD210 and Wardell et al 2015a).

Anti-tumour activity

Anti-tumour Activity in *In vitro* Models

Elacestrant was evaluated for anti-tumour activity in several *in vitro* ER-positive breast cancer models. Antiproliferative effects of elacestrant were evaluated in MCF-7 and CDK4/6iR cell lines (Reports 17RAD2022, RAD-002, 18RAD2023, and 19RAD2034).

MCF-7 cells treated with E2 showed a dose-dependent increase in proliferation, with an EC50 of 0.004 nM. MCF-7 cells treated with 10, 100, or 1000 nM elacestrant decreased basal rates of cell proliferation, with an IC50 of 5.6 nM. Co-treatment of cells with elacestrant and E2 resulted in a dose-dependent decrease in E2-induced proliferation, with IC50 values for elacestrant of 4.2 and 27 nM, in the presence of 0.01 and 0.1 nM E2, respectively. Similarly, treatment of MCF-7 cells with S-1901 decreased basal rates of cell proliferation, but with an IC50 of 99 nM in the absence of E2 and IC50 of 120 and 820 nM in the presence of 0.01 or 0.1 nM E2, respectively. Thus, in the presence of E2, 300-400 higher levels of elacestrant are required to obtain 50% ERα inhibition. Both elacestrant and S-1901 with or without E2 were not able to stimulate MCF-7 proliferation at any dose (report RAD-002).

Figure 2 and Figure 3**: Effects of elacestrant on MCF-7 cell proliferation without or with 10 pM E2 (Study RAD-002)**

Figure 2

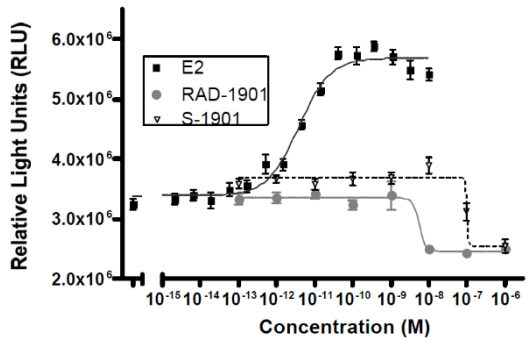
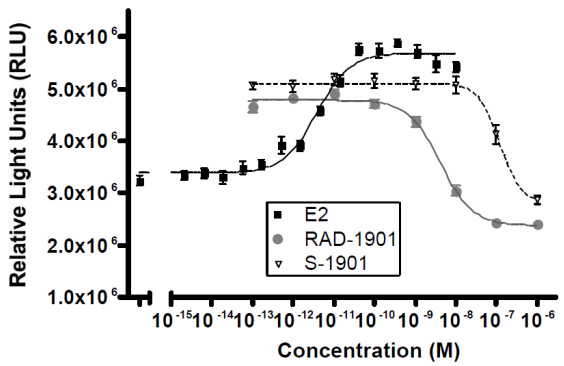


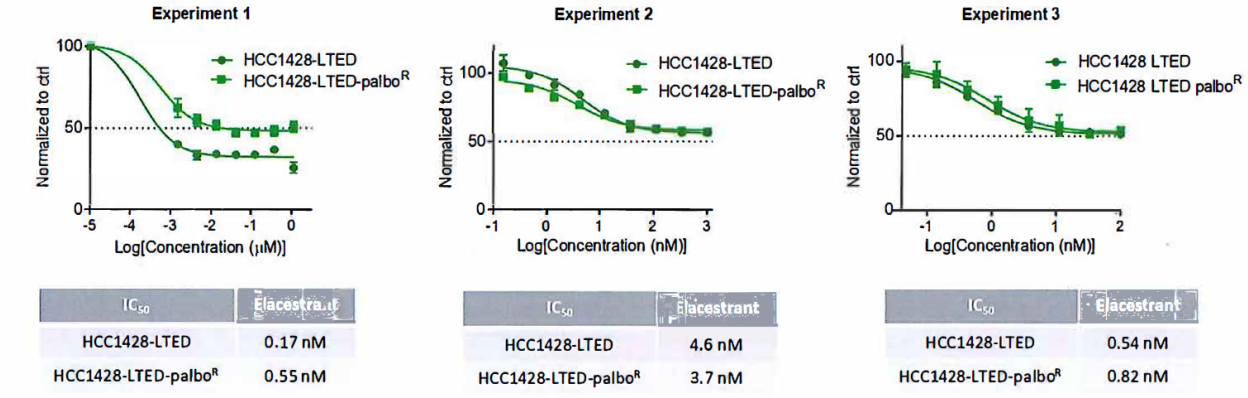
Figure 3



E2 = oestradiol; RAD-1901= elacestrant; S-1901= S-enantiomer of elacestrant. Source: Report RAD-002

To investigate the antiproliferative effects of elacestrant in models that mimic post-aromatase inhibitor (AI) and post-AI-CDK4/6 inhibitor settings, an ER-positive cell line was oestrogen-deprived long term (HCC1428-LTED) to model progression on AIs. In addition, a palbociclib-resistant derivative of the cells (HCC1428-LTED-palboR) was developed by propagating HCC1428-LTED cells long-term (7 to 13 months) in the presence of increasing concentrations of palbociclib (up to 500 nM) to model progression on CDK4/6 inhibitors. Elacestrant (incubated for 7 days up to 1000 nM) inhibited the growth of palbociclib-sensitive (HCC1428-LTED) and palbociclib-resistant (HCC1428-LTED-palboR) cell lines. The mean IC50 of growth inhibition mediated by elacestrant in palbociclib-sensitive and palbociclib-resistant cells was 1.77 and 1.69 nM, respectively.

Figure 4: Elacestrant-induced growth inhibition of HCC1428-LTED and HCC1428 LTED-palboR cell lines (Study 18RAD2023)



IC_{50}	Elacestrant
HCC1428-LTED	0.17 nM
HCC1428-LTED-palbo^R	0.55 nM

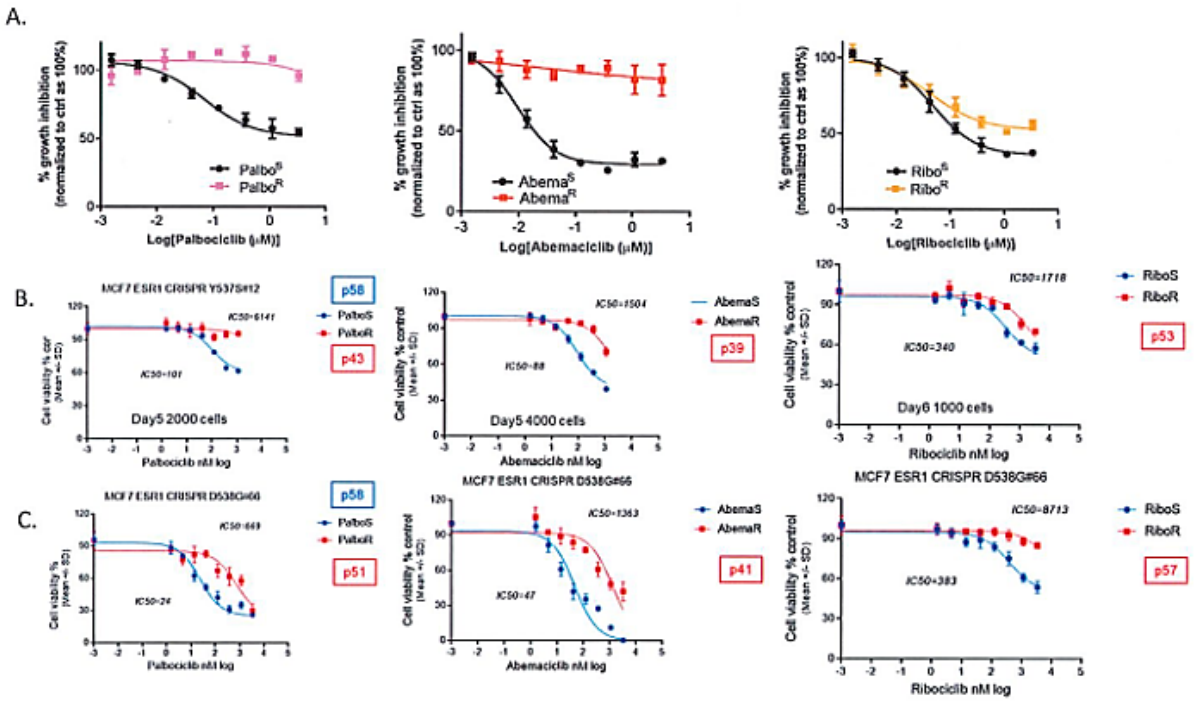
IC_{50}	Elacestrant
HCC1428-LTED	4.6 nM
HCC1428-LTED-palbo^R	3.7 nM

IC_{50}	Elacestrant
HCC1428-LTED	0.54 nM
HCC1428-LTED-palbo^R	0.82 nM

IC_{50} = half-maximal inhibitory concentration. Source: Report 18RAD2023

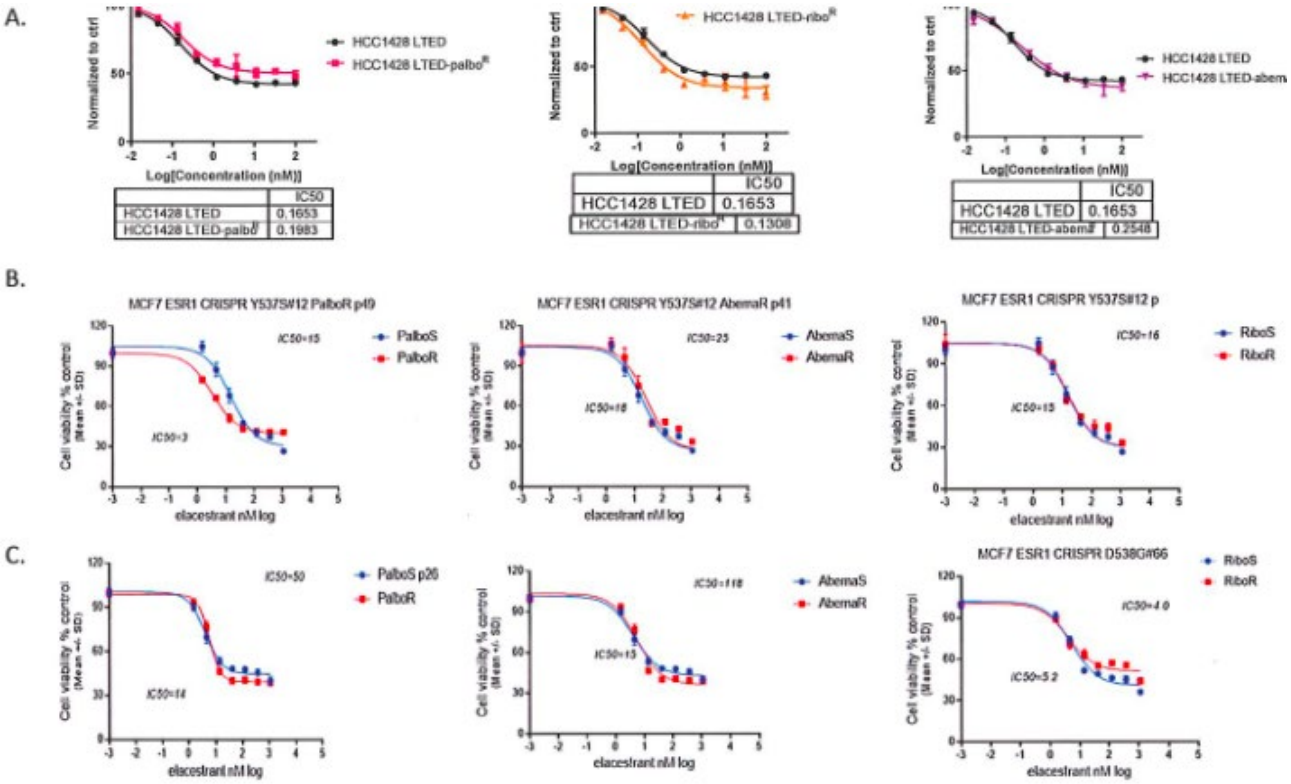
The antiproliferative effects of elacestrant were also investigated in models that represent ESR1 wild type (HCC1428-long-term oestradiol deprivation [LTED]) and ESR1 mutant (MCF7-Y537S and MCF7-D538G) CDK4/6iR cells. CDKiR derivatives of the cells were developed by propagating the cells long term (7 to 10 months) in the presence of increasing concentrations of CDK4/6 inhibitors (up to 1,000 nM) to model progression on CDK inhibitors, palbociclib (Palbo), ribociclib (Ribo), and abemaciclib (Abema). Cells were incubated with CDK inhibitors and elacestrant for 7 days and assayed using the Cell Titer-Glo assay using luminescence as read-out. IC50 values for CDK4/6 inhibitors were significantly increased in CDK4/6iR cells compared to their parental CDK4/6iS cells. However, the extent of growth inhibition (which was partial) and potency of elacestrant was similar in the CDK4/6iS and the CDK4/6iR cells, which was also confirmed by Western blot analysis that measured similar reduction in expression of ERα by elacestrant in CDK4/6iS and CDK4/6iR cells (Report 17RAD2022).

Figure 5: Growth of HCC1428-LTED-CDK4/6 inhibitor-resistant and -sensitive, MCF7-Y537S, and MCF7-D538G cells in the presence of CDK4/6 inhibitors



Ten months post cells crowing in the medium containing CDK4/6 inhibitors, the HCC1428-LTED-CDK4/6 inhibitor resistant (A), the MCF7-Y537S (B), and the MCF7-D538G (C) cells exposed to CDK4/6 inhibitors in proliferation assays. Inhibition plots were graphed by GraphPadPrism 7.0. Data are represented as mean ± standard deviation.

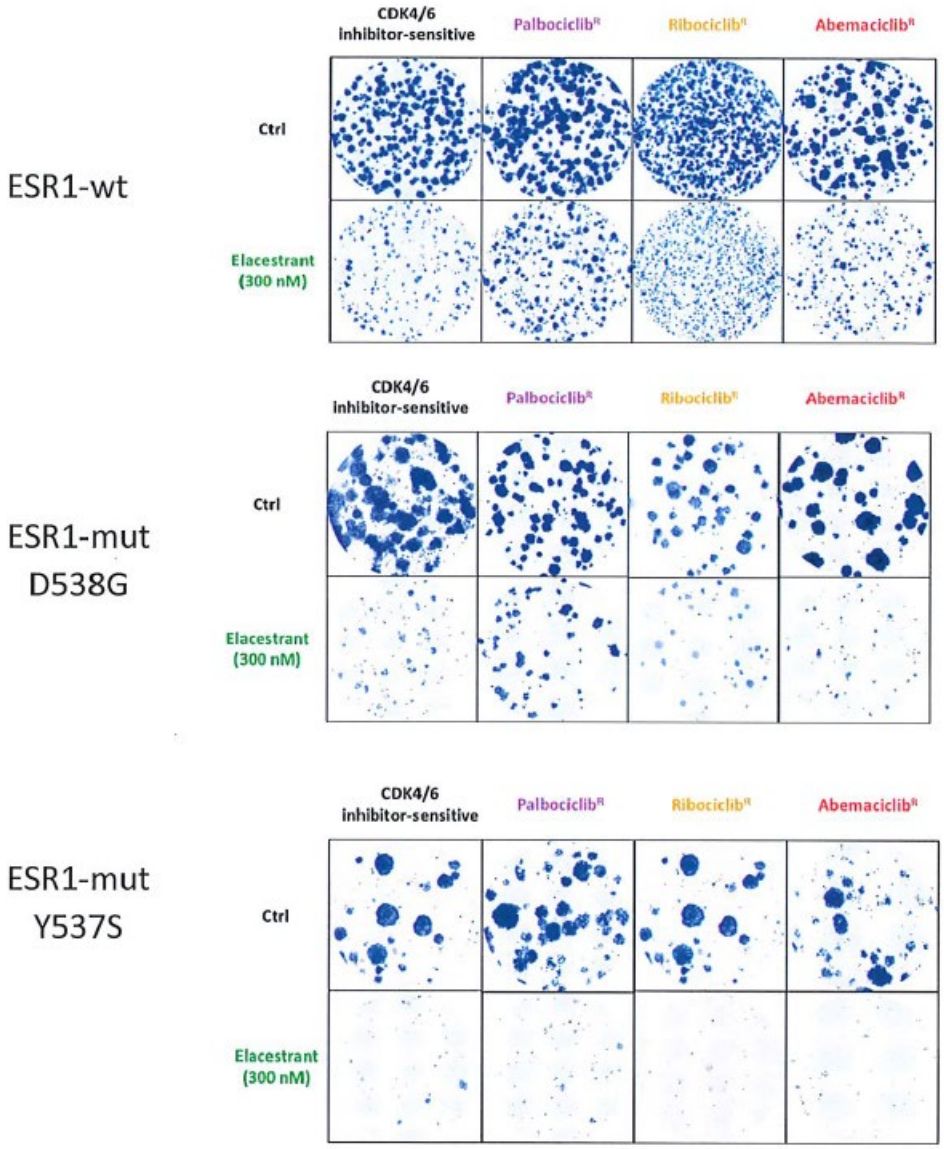
Figure 6: Inhibition of HCC1428-LTED-CDK4/6 inhibitor-resistant, MCF7-Y537S and MCF7-D538G cells in the presence of elacestrant



ESR1 wild-type (A) and *ESR1* mutant (Y537S [B] and D538G [C]) cells exposed to elacestrant in proliferation assays. Inhibition plots were graphed by GraphPadPrism 7.0. Data are represented as mean ±(standard deviation).

In another study (19RAD2034), patient populations with mutant ER which is AI-resistant were mimicked by ER-positive cell lines (MCF-7) that were engineered to express mutant ESR1Y537S and ESR1D538G to model progression on AIs. Additionally, an ER-positive cell line harbouring wild-type ER (HCC1428) was oestrogen deprived long-term (HCC1428-LTED) to model progression on AIs. CDK4/6iR derivatives of the cells were also developed by propagating the cells long-term (7 to 10 months) in the presence of increasing concentrations of CDK4/6 inhibitors. Elacestrant partially inhibited the growth of HCC1428-LTED, MCF7-Y537S, and MCF7-D538G cells, which proliferated in the absence of oestrogen. Palbociclib, ribociclib, and abemaciclib did not inhibit colony formation of their respective CDK4/6iR cell lines. However, elacestrant (300 nM) inhibited colony formation of both CDK4/6iS and CDK4/6iR breast cancer cells when compared to vehicle control-treated cells. The growth inhibitory effect observed was independent of ESR1 status (wild-type or mutant) and the CDK4/6 inhibitor used to develop resistance (Report 19RAD2034).

Figure 7: Elacestrant efficacy in CDK4/6iS and CDK4/6iR cells (Study 19RAD2034)



CDK4/6 = cyclin-dependent kinase 4/6; ctrl = control; ESR1-mut = oestrogen receptor 1 mutation; ESR1-wt = oestrogen receptor 1 wild-type; R = resistant. Source: Report 19RAD2034

In vivo Models

Elacestrant was evaluated for anti-tumour activity in several *in vivo* ER-positive breast cancer models. Tumour growth inhibition by elacestrant was assessed in an oestrogen responsive MCF-7 human breast carcinoma (Reports 15RAD246, 14RAD028, 14RAD019, and 15RAD219) and multiple nude mouse PDX models, using cells insensitive to fulvestrant and CDK4/6 inhibitors and cells harbouring mutations in ESR1 gene (Reports 16RAD240, 16RAD227, 18RAD217, 17RAD211, 18RAD203, 15RAD205, 18RAD202, 17RAD208, 16RAD225-2, and 16RAD225-1).

MCF-7 xenografted tumour models

In study 15RAD246 female Balb/c mice were inoculated subcutaneously with MCF-7 tumour cells (10×10^6). Three days prior to cell inoculation, E2 (0.18 mg) pellets were implanted subcutaneously to stimulate tumour growth. Once tumours reached a volume of approximately 145 mm^3, mice were treated with 30, 60, and 120 mg/kg elacestrant, which resulted in significant anti-tumour activity with

tumour growth inhibition (TGIs) of 100.5%, 103.4%, and 103.6% on Day 28, respectively. In the mice that survived until 56 days, mean tumour size was 92.3%, 91.4%, and 93.4% smaller, respectively, on Day 28, and 95.2%, 95.8%, and 96.0% smaller, respectively, on Day 56. Similar anti-tumour activity was shown for the positive controls, i.e., the bazedoxifene and fulvestrant treatment groups.

In study 15RAD219 female Balb/c nude mice were inoculated subcutaneously with MCF-7 tumour cells (10×10^6). Three days prior to cell inoculation, E2 (0.18 mg) pellets were implanted subcutaneously to stimulate tumour growth. Seven days after tumour cell implantation, the average tumour size was 194 mm^3. Significant dose-dependent anti-tumour activity on Day 27 was observed in mice treated with elacestrant at 30 and 60 mg/kg with mean tumour volumes of 226 mm^3 (TGI = 96%) and 168 mm^3 (TGI = 103%) and as well in mice treated with fulvestrant, Palbociclib induced TGIs of 66%, 66%, and 64%, respectively. When compared with 30 mg/kg elacestrant alone, the combination of 30 mg/kg elacestrant + 45 mg/kg palbociclib produced better anti-tumour efficacy (TGI = 113% [$p < 0.05$]), but 30 mg/kg elacestrant + 2.5 mg/kg everolimus did not. When compared with 60 mg/kg elacestrant single-agent treatment, both 60 mg/kg elacestrant + 45 mg/kg palbociclib and 60 mg/kg elacestrant + 2.5 mg/kg everolimus combinations produced better anti-tumour efficacy (TGI = 116% [$p < 0.05$] and TGI = 115% [$p < 0.05$], respectively).

In study 14RAD028, female athymic nude mice were inoculated subcutaneously with MCF-7 tumour cells and E2 (0.36 mg) pellets were implanted subcutaneously to stimulate tumour growth. In MCF-7 tumour-bearing mice treated with elacestrant at 30 and 60 mg/kg, significant anti-tumour activity was reported with TGIs of 66% and 88% on Day 40, respectively. Similar anti-tumour activity was also observed in tamoxifen and fulvestrant treatment groups.

In study 14RAD019, female athymic nude mice were inoculated subcutaneously with MCF-7 tumour cells and E2 (0.36 mg) pellets were implanted subcutaneously to stimulate tumour growth. For MCF-7 tumour-bearing mice treated with elacestrant at 60, 90, and 120 mg/kg, significant anti-tumour activity was reported with TGIs of 94%, 97%, and 96% on Day 42, respectively. Significant anti-tumour activity was also observed in tamoxifen and fulvestrant treatment groups. Partial regressions were observed in mice that received elacestrant (60, 90, and 120 mg/kg), tamoxifen, and fulvestrant.

To study the potential ability to cross the blood-brain barrier, an MCF-7 intracranial tumour xenograft model was used (Garner et al 2015). Survival was the primary endpoint to evaluate antitumour activity. Female athymic nude mice were implanted intracranially with MCF-7 tumour cells (1×10^6) accompanied by subcutaneously implanted E2 (0.36 mg) pellets (to stimulate tumour growth). Five days post tumour cell implantation, animals were treated with 120 mg/kg/day elacestrant orally or 0.5 mg/day fulvestrant subcutaneously for 54 days. In this orthotropic model, E2-dependent breast cancer cells (MCF-7) implanted into the brain led to rapid tumour growth and high mortality in untreated animals. Elacestrant resulted in anti-tumour activity and prolonged survival while fulvestrant, an agent known to be ineffective at crossing the blood-brain barrier, had a limited effect in reducing mortality.

Patient derived xenograft (PDX) models

The anti-tumour effect of elacestrant was evaluated in multiple nude mouse PDX models, using cells insensitive to fulvestrant and CDK4/6 inhibitors and cells harbouring mutations in ESR1 gene (Reports 16RAD240, 16RAD227, 18RAD217, 17RAD211, 18RAD203, 15RAD205, 18RAD202, 17RAD208, 16RAD225-2, and 16RAD225-1).

In study 16RAD240, female athymic nude mice, implanted with tumour fragments from ST941/HI harvested from host animals, were treated with elacestrant at 10, 30, and 60 mg/kg for 62 days. Significant anti-tumour activity was reported with TGIs of 72%, 84%, and 93% on Day 26 (max.

tumour size was reached in untreated mice), respectively. Fulvestrant treatment did not result in significant anti-tumour activity relative to the vehicle control.

In Study 16RAD227, female athymic nude mice, implanted with tumour fragments from ST941/HI harvested from host animals, were treated with at 10 and 30 mg/kg elacestrant for 60 days. Significant anti-tumour activity was reported with TGIs of 73% and 101% on Day 39, respectively. Ribociclib displayed a limited effect in this model, and alpelisib treatment did not result in significant anti-tumour activity relative to the vehicle control. Partial regressions were observed in 3 mice that received elacestrant (30 mg/kg) and in 1 mouse treated with alpelisib.

In study 18RAD217, OVX immune-deficient female mice (Report 18RAD217) inoculated with tumour fragments from ST941/HI/FSR/PBR (18RAD217), functioning as a re-derived hormone-independent (HI) START PDX model representing human ER+, ESR1 mutant breast cancer, were evaluated for anti-tumour effect of elacestrant alone (30 mg/kg) and a combination of Palbociclib (30mg/kg) and fulvestrant (5 mg/kg). All agents were tolerated at the dose levels used, and elacestrant was active towards the ST941/HI/FSR/PBR model in OVX female nude mice and seems more effective as compared to combination treatment of Palbociclib and fulvestrant (TGI of 74 % vs 24%).

In study 18RAD203, female athymic nude mice were implanted with tumour fragments from ST2535/HI (START PDX model designated ST2535/HI) representing human ER-positive ESR1 mutant (ESR1D538G) breast cancer. Significant anti-tumour activity was reported with TGIs of 88% and 91% on Day 60, respectively. Fulvestrant (5 mg/dose) treatment also resulted in TGI of 44%. In study 17RAD211, using the same model, following 37 days of treatment with elacestrant 30 and 60 mg/kg, a TGI of 87 and 100% was shown, respectively and the tumours did not re-grow until 3 weeks after dosing was terminated.

In study 15RAD205, a PDX model using female athymic nude mice were implanted with tumour fragments from ST986 or ST2177 harvested from host animals. ST986 expresses wild-type ER and progesterone receptor, and ST2177 harbours a Y537S mutation in the ESR1 gene (the most frequently reported aberrations found in tumours from patients treated with AIs also resulting in high levels of constitutive ER signalling). Upon elacestrant at 30, 60, and 120 mg/kg, significant anti-tumour activity was reported in both models up to Day 61. Fulvestrant treatment resulted in significant anti-tumour activity in both models at a dose of 5 mg (TGI: 104 %), but was inactive in ST986 tumour-bearing mice at a dose of 1 mg. In ST2177 tumour-bearing mice, tamoxifen showed significant anti-tumour activity (TGI: 105%). Partial regressions were observed in ST986 tumour-bearing mice that received elacestrant (30, 60, and 120 mg/kg) and fulvestrant (5 mg/dose) and in ST2177 and ST986 tumour-bearing mice that received elacestrant (60 and 120 mg/kg) and tamoxifen. Elacestrant was well tolerated at doses up to 120 mg/kg.

In study 18RAD202, female athymic mice were implanted with tumour cells ST3932 (tumour cells with PIK3CA mutations, from a 62-year-old woman pre-treated with tamoxifen, fulvestrant/palbociclib, and paclitaxel), representing ER-positive cells with a moderate sensitivity to both ribociclib and abemaciclib. In ST3932 tumour-bearing mice treated with elacestrant at 30 and 60 mg/kg, significant anti-tumour activity was reported with TGIs of 62% and 52% on Day 35, respectively. Similar anti-tumour activity was observed for the palbociclib, alpelisib, and fulvestrant treatment groups.

In study 17RAD208, female athymic nude mice were implanted with WHIM43 tumour cells. These tumour cells harbour an ESR1D538G mutation, are resistant to palbociclib *in vivo* and lack retinoblastoma protein expression, which makes them resistant to CDK4/6 inhibitors (Wardell et al 2015b). In WHIM43 tumour-bearing mice treated with elacestrant at 30 and 60 mg/kg, significant anti-tumour activity was reported with TGIs of 65% and 78% on Day 55, respectively. Fulvestrant and palbociclib treatment did not result in significant anti-tumour activity relative to the vehicle control.

In study 16RAD225-2, athymic nude mice were implanted with Champions Tumour Graft human mBC model (CTG-1211, a breast cancer cell line with mutant ESR1D538G from a patient with prior tamoxifen, fulvestrant, and AI therapy). CTG-1211 tumour-bearing mice treated with elacestrant at 30 and 60 mg/kg, significant anti-tumour activity was reported with TGIs of 55% and 65% on Day 35, respectively. Fulvestrant treatment did not result in significant anti-tumour activity relative to the vehicle control.

In study 16RAD225-1, athymic nude mice were implanted with a low-passage Champions Tumour Graft (CTG) to establish a human mBC model. CTG-1260 is a breast cancer cell line that is ER-positive/progesterone receptor-positive/HER2-negative and includes PIK3CA mutations at D530G and H1047R, and an ESR1 mutation at D538G). In CTG-1260 tumour-bearing mice treated with elacestrant at 30 and 60 mg/kg, significant anti-tumour activity was reported with TGIs of 53% and 77% on Day 79, respectively. Fulvestrant treatment did not result in a statistically significant anti-tumour activity relative to the vehicle control but gave a similar response as 30 mg/kg elacestrant.

Pharmacokinetics in pharmacology studies

Pharmacokinetics was not directly assessed in these studies. However, in support of pharmacology mouse tumour model studies, a non-GLP study was conducted to evaluate the PK of elacestrant after once daily oral doses for 1 week and the PK of fulvestrant after once weekly SC doses for 2 weeks in mice (Report 16RAD205). Following oral administration of elacestrant for up to 8 days at doses of 30, 60, and 120 mg/kg QD, exposure, as assessed by Cmax, was 180 to 347, 556 to 750, and 1530 ng/mL, respectively, and AUC0-24 was 1490 to 2330, 3740 to 4950, and 12,200 ng•hr/mL, respectively.

2.5.2.2. Secondary pharmacodynamic studies

In vitro secondary pharmacodynamics studies were conducted to evaluate the biochemical target selectivity of elacestrant and the binding affinity of elacestrant to CNR1, CNR2, and ADRA2A. *In vivo* studies were conducted to evaluate the uterotrophic effects of elacestrant in female mouse and rat pups and in OVX rats. Elacestrant was further assessed by evaluating its ability to regulate LH release and prevent bone loss. Additionally, the effects of elacestrant on vasomotor instability were also assessed *in vivo*.

Biochemical Target Assays

In study 1035439, 1035745 and 10RAD005 binding and activity of elacestrant towards a wide panel of 166 molecular targets was evaluated and in these studies, elacestrant at 1 µM presented > 50% inhibition for CNR1 (cannabinoid receptor, 99% inhibition), ERβ (98% inhibition), growth hormone secretagogue (GHS, ghrelin; 51% inhibition), motilin (71% inhibition), and somatostatin sst1 (52% inhibition) receptors. The maximum estimated unbound concentration of elacestrant in human plasma was approximately 2.09 ng/mL (assuming approximately 99% protein binding), corresponding to 4.6 nM, on Day 7 for a 500 mg dose QD (Conlan et al 2020).

Cannabinoid Receptor

In study 09RAD043, activity of elacestrant against CNR1 and CNR2 was assessed in a whole cell-based assay and elacestrant appeared devoid of agonist activity and possessed only a weak antagonist-like activity at this receptor (IC50 = 2 µM). Elacestrant (up to 3 µM) did not suppress forskolin-stimulated cAMP in either CNR1- or CNR2-expressing cells. In antagonist mode, elacestrant did not mitigate cAMP suppression by WIN55212-2, a known CNR1 and CNR2 agonist. The maximum estimated unbound

concentration of elacestrant in human plasma was approximately 2.09 ng/mL (assuming approximately 99% protein binding), corresponding to 4.6 nM, on Day 7 for a 500 mg dose QD (Conlan et al 2020).

Adrenergic Receptor α2a

In study 10RAD005, functional activity of elacestrant against ADRA2A was assessed in 3 cell-based assays: 1) guanosine triphosphate (GTP)γS binding assay, 2) cAMP assay, and 3) Gqo CHO-K1 reporter assay. Each assay was unique in that it examined ADRA2A signalling at different points in the signalling cascade. In assay 1 it was shown that treatment of elacestrant in the GTPγS binding assay did not cause an increase or decrease of GTP binding and the EC50 and IC50 were estimated to be > 10,000 nM. In assay 2, the cAMP assay, elacestrant did not suppress forskolin-induced cAMP at concentrations up to 100 nM and therefore the EC50 was determined to be > 100 nM. In assay 3, evaluating the antagonist mode, elacestrant did not mitigate the UK14304 suppression of forskolin-stimulated cAMP. Consistent with results from GTPγS binding and the cAMP assays, the EC50 and IC50 for elacestrant agonist and antagonist activity was estimated to be > 3000 nM.

Effects on Uterine Tissue

In study 14RAD020, female CD-1 mice (juvenile, 18 to 21 days old), the effect of elacestrant on the uterus was compared with E2, tamoxifen, and raloxifene. Elacestrant administered at ≥ 0.1 mg/kg/day resulted in decreases of endometrial surface epithelium thickness and decreased uterine weights both not dose-dependent. The administration of E2 (at 0.01 and 0.3 mg/kg/day) resulted in uterotrophic effects as reflected by significant increased uterus weight. Raloxifene administration at 1 and 10 mg/kg/day resulted in decreased uterine weights.

In study 14RAD022, in female Sprague Dawley rats (juvenile, 21 to 24 days old), the effect of elacestrant on the uterus was compared with E2, tamoxifen, or raloxifene. Results from this study indicated that elacestrant treatment led to decreased uterine thickness/weights at ≥ 1 mg/kg/day, whereas E2, tamoxifen, and raloxifene increased the thickness of the endometrial epithelium. Only E2 increased uterus weight.

In study RAD-003, uterotrophic effect of elacestrant was assessed in immature female Sprague Dawley rats by assessing changes in uterine weight, histology, and C3-complement gene expression. Elacestrant showed no agonist activity in the uterus of the immature rat at doses up to 100 mg/kg. Elacestrant was found to have no significant effect on uterine weight. Elacestrant (0.1 to 10 mg/kg) dose-dependently antagonized the uterotrophic effects of E2, while having no agonist-like effect up to the highest dose tested (100 mg/kg). Microscopic analysis of elacestrant-treated animals (100 mg/kg) confirmed the absence of morphological changes in the endometrial epithelium compared with the vehicle. Elacestrant did not result in a change in C3-complement gene expression. In conclusion, elacestrant, unlike E2, raloxifene, or tamoxifen, did not stimulate the uterus, but antagonized oestrogen action on the uterus.

Effects on Luteinizing Hormone Release

In study RAD-008, the activity of elacestrant to regulate LH release was evaluated in OVX female Wistar rats that have decreased endogenous oestrogen and elevated serum LH level.

Table 6: Study Design (Report RAD-008)

Treatment (vehicle)	**No. of animals/ group/dose level**	**Dose (mg/kg)**	**Dosing route**	**Dosing schedule**
Vehicle (DMSO:Tween-80 [65:35])	9	0	Intraperitoneal	QD for 3 days

Treatment (vehicle)	No. of animals/ group/dose level	Dose (mg/kg)	Dosing route	Dosing schedule
Elacestrant (DMSO:Tween-80 [65:35])	6	1 and 10	Intraperitoneal	QD for 3 days
Oestradiol benzoate (EB) (DMSO:Tween-80 [65:35])	6	0.01	Subcutaneous	QD for 3 days

DMSO = dimethyl sulfoxide; No. = number; QD = once daily.
Source: Report RAD-008

At doses of 1 and 10 mg/kg, elacestrant treatment showed a weak oestrogen-like agonist activity by decreasing serum LH (40% inhibition as compared with 85% by EB), reaching statistical significance at the 10 mg/kg dose level ($p = 0.008$) compared with vehicle. The inhibitory effect displayed by elacestrant was less than that of oestradiol benzoate (EB).

Effects on Ovariectomized Rat Osteoporosis Model

In study RAD-004, OVX or SHAM surgery (SHAM) were treated with elacestrant and E2 for 4 wks. Elacestrant was well tolerated at doses up to 3 mg/kg. OVX rats treated with elacestrant ≥ 0.1 mg/kg showed a dose-dependent reduction in OVX-induced body weight gain. E2 had a similar effect on decreasing OVX-induced weight gain. Elacestrant and E2 treatment prevented OVX-induced bone loss and also preserved bone microarchitecture. Compared to OVX, uterine wet weights in rats administered elacestrant were slightly higher and approximately 25% of the weight of the SHAM animals, whereas E2 increased uterine weight as compared to OVX alone to a level similar to the SHAM group (68% of the weight of the SHAM animals).

In study RAD-006, female Fischer rats that had undergone either OVX or SHAM were treated with elacestrant or E2 for 8 wks. Elacestrant prevented OVX-induced bone loss at dose levels as low as 0.1 mg/kg, while preserving bone microarchitecture. This protection against bone loss was achieved in part by a reduction in bone resorption, as demonstrated by a reduction in urinary deoxypyridinoline at 4 weeks. Additionally, elacestrant treatment decreased plasma cholesterol levels, and there was no uterine stimulation.

Vasomotor Symptoms

In study RAD-005, the effect of elacestrant on vasomotor responses were evaluated in a morphine-dependent rat model by measuring naloxone-induced change in tail-skin temperature (TST).

Table 7: Study Design (Report RAD-005)

Treatment (vehicle)	No. of animals/ group/dose level	Dose (mg/kg)	Dosing route	Dosing schedule
OVX + vehicle (5% DMSO/95% sesame oil)	8	0	Subcutaneous	Single dose
OVX + elacestrant (DMSO/Tween-80: water [13:7:80])	8 to 9	0.01, 0.1, and 1	Subcutaneous	Single dose

Treatment (vehicle)	No. of animals/ group/dose level	Dose (mg/kg)	Dosing route	Dosing schedule
OVX + EE (DMSO/Tween-80: water [13:7:80])	10	0.1	Subcutaneous	Single dose

DMSO = dimethyl sulfoxide; EE = 17-α-ethinyl oestradiol; No. = number; OVX = ovariectomy.
Source: Report RAD-005

Both EE (17-α-ethinyl oestradiol) and elacestrant (0.1 and 1 mg/kg) significantly abated the naloxone-induced flush, with no significant difference in TST change observed between EE and elacestrant (1 mg/kg).

2.5.2.3. Safety pharmacology programme

In vivo and *in vitro* safety pharmacology studies were performed to assess the cardiac safety, respiratory effects, and neurological effects of elacestrant. Other safety pharmacology studies investigated the effects of elacestrant on bleeding time, wound healing, and the gastrointestinal system.

- **Cardiovascular System *In Vitro* and *In Vivo***

In Vitro

Study 7801-126

An *in vitro* GLP study was conducted to evaluate the effects of elacestrant on hERG (stably transfected in human embryonic kidney [HEK]-293 cell line) channel current, a surrogate for I_{Kr}, the rapidly activating delayed rectifier cardiac potassium current (Report 7801-126). The inhibition of hERG channel current is commonly used to identify the potential of compounds to induce QT (total depolarisation and repolarisation time) prolongation and, ultimately, the malignant arrhythmia Torsade de Pointes. Four concentrations of elacestrant (0.1, 0.3, 0.6, and 1 µM) were used to determine the hERG effects(s). *In vitro* effects of elacestrant in a stably transfected HEK-293 cell line were evaluated at elacestrant concentrations from 0.1 to 1 µM. The nominal IC_{50} for the inhibitory effect of elacestrant on hERG potassium current was 0.41 µM (407 nM) (Hill coefficient = 2.3).

Study 7801-131

The effect of elacestrant on cardiac action potentials was evaluated in an *in vitro* GLP study using isolated rabbit Purkinje fibres (Report 7801-131). Purkinje fibres were isolated from 8 female New Zealand White rabbits. Studies were conducted at physiologic temperature (37ºC). After stabilisation, 4 fibres were exposed to the vehicle first, then to increasing concentrations of elacestrant, for 20 minutes each, before stimulation at basic cycle lengths of 1.0 and 0.5 seconds. These basic cycle lengths correspond to *in vivo* heart rates of 60 and 120 beats/minute, respectively. The 3 concentrations of elacestrant used were 0.1, 1, and 10 µM (clinically equivalent to 46, 459, and 4586 ng/mL), and a parallel vehicle control was evaluated. At the end of the vehicle exposure period, a positive control, dl-sotalol (50 µM), was applied. Electrophysiology parameters collected included resting membrane potential (RMP; mV), action potential amplitude (APA; mV), maximum rate of rise (V_{max}; V/s), action potential duration at 60% repolarisation (APD_{60}; ms), and APD_{90} (ms).

No significant physiological effects were noted at elacestrant concentrations of 0.1 and 1 µM at stimulation frequencies mimicking heart rates of 60 and 120 beats/minute. At the 10 µM concentration, electrical stimulation failed to elicit action potentials in 2 of the 4 fibres. Thus,

assessment of the electrophysiologic effects of elacestrant in these 2 fibres was not possible. In the 2 fibres that responded to the electrical field stimulation, 10 µM elacestrant decreased APA at a stimulation frequency equivalent to 60 beats/minute. At a stimulation frequency equivalent to 120 beats/minute, these 2 fibres demonstrated a decrease in all electrophysiology parameters except for RMP, which was increased. For comparison, dl-sotalol increased APD_{60} and APD_{90} by 32% and 35%, respectively, at basic cycle lengths of 0.5 seconds and by 52% and 54%, respectively, at basic cycle lengths of 1.0 second.

Elacestrant showed a concentration-dependent inhibition of hERG channel current at concentrations from 0.1 to 1 µM, with an IC_{50} of 0.41 µM (407 nM). However, at the 1 µM concentration, which produced an 86.8% I_{Kr} blockade in the hERG assay, there were no significant action potential changes in APD_{60}, APD_{90}, RMP, or V_{max} at both stimulation frequencies. At 10 µM, a decrease of APA was detected at stimulation frequencies mimicking heart rates of 60 beats/minute, whereas a decrease of APA, APD_{60}, APD_{90}, and V_{max} and an increase of RMP was recorded at stimulation frequencies mimicking heart rates of 120 beats/minute.

In Vivo

The cardiovascular safety of elacestrant was evaluated in an *in vivo* GLP 4-dose crossover study in cynomolgus monkeys (7801-118). Eight naïve female cynomolgus monkeys were assigned to treatment groups using a 4 × 4 Latin square crossover design. Each animal received 1 of 4 doses on Days 1, 4, 8, and 11 of the dosing phase. Assessment of cardiovascular function was based on hemodynamic measurements (heart rate and blood pressure) measurements, cardiac inotropy (dP/dt_{max}), and ECG parameters (ECG measurements including QRS, RR, QT, and rate corrected QT intervals) evaluated predose and approximately 1, 2, 4, 8, 12, and 24 hours postdose on each dosing day. Mortality, clinical signs (including qualitative food consumption), body weights, intra-abdominal body temperature (via telemetry), and clinical pathology evaluations were assessed.

All animals survived through the in-life period. Elacestrant-related clinical signs included emesis in 4/8 animals and liquid faeces in 3/8 animals following the administration of 100 mg/kg elacestrant. Elacestrant administration produced no adverse hemodynamic or ECG effects in 8 female cynomolgus monkeys at oral doses up to 50 mg/kg and only modest changes at the 100 mg/kg dose. All ECGs were within normal limits at doses up to 100 mg/kg. The PR interval of the ECG was decreased (6% to 11% relative to time-matched controls) at doses ≥ 50 mg/kg, while QRS duration was increased (by approximately 10% relative to time-matched vehicle controls) in the 100 mg/kg group. Significant ($p \leq 0.05$) elacestrant-related changes in cardiovascular telemetry data included increases in covariate-adjusted mean diastolic (11%), systolic (6%), and mean arterial pressures (8%) at one hour post-dose in animals given 100 mg/kg. Covariate-adjusted mean heart rate was significantly higher than time-matched vehicle control in animals given 100 mg/kg at 1 (10% increase), 2 (14% increase), and 4 (22% increase) hours post-dose. Heart rate changes were reversible.

ECG measurements including QT(c) in repeated dose toxicity studies, during which monkeys were exposed to elacestrant for 4 weeks up to 50 mg/kg or for 39 weeks up to 30 mg/kg, did not show cardiac effects.

A comparison of *in vitro* hERG inhibition (IC50 187 ng/mL) and estimated unbound elacestrant concentration of 2.7 ng/mL in monkey plasma at 50 mg/kg (a dose that was shown to be devoid of any QT interval effects) showed an approximately 69-fold safety margin. These data showed that elacestrant has a low risk for adverse cardiovascular effects at the human therapeutic dose level, as the maximum estimated unbound concentration of elacestrant in human plasma was approximately 2.09 ng/mL (assuming approximately 99% protein binding) on Day 7 for a 500 mg dose QD (Conlan et al 2020).

- **Respiratory system**

The respiratory safety of elacestrant was evaluated *in vivo* in a GLP oral dose study (7801-119) in Sprague-Dawley rats. Twenty-four female Sprague-Dawley rats were assigned to treatment groups. Assessment of respiratory function was based on analysis of respiratory rate, tidal volume, and minute volume at 1, 2, 3, 4, 5, 6, and 24 hours post-dose. Baseline data were collected for at least 1 hour on a day prior to dosing. No significant effect, and no biologically relevant differences were detected in respiratory rate, tidal volume, or minute volume at any measured time point relative to concurrent vehicle group and predose values in female rats given a single dose of 25, 50, or 100 mg/kg elacestrant via oral gavage. No clinical signs of toxicity were observed during the study. All animals survived until scheduled sacrifice. Elacestrant does not affect the respiratory system.

- **Central nervous system**

The neurological safety of elacestrant was evaluated *in vivo* in a GLP oral dose study (7801-120) in Sprague-Dawley rats. Twenty female Sprague-Dawley rats were assigned to treatment groups. After dosing, animals were observed postdose for 5 days to assess the reversibility, persistence, or delayed occurrence of any effects. Assessment of neurotoxicity was based on mortality, clinical signs, body weight, and a modified Irwin battery of neurological assessments, including cage side, hand held, open field, and elicited response observations.

All animals that received elacestrant survived until scheduled sacrifice. No abnormal observations for the elicited responses in the modified Irwin screen. Body temperature, nociceptive reflex, forelimb grip strength, and hind limb grip strength were similar and not significantly altered by administration of 25, 50, or 100 mg/kg elacestrant, relative to the response observed with animals given vehicle or during pre-dose baseline screens.

- **Other organ systems**

Bleeding time assessment

In study 14RAD009 (GLP) the potential effect of elacestrant on bleeding time was evaluated. Forty male and female Sprague-Dawley rats (5 animals/sex/group) were assigned to treatment groups. Cutaneous bleeding time was assessed at least 1 hour post-dose on Day 7. The bleeding time was measured at intervals of 2 minutes until bleeding ceased. Additional parameters and endpoints evaluated throughout the study included clinical signs, body weights, body weight changes, and food consumption. Warfarin was administered as a positive control drug.

Once daily oral administration of elacestrant 20 and 50 mg/kg/day was well tolerated in rats. No elacestrant-related mortalities occurred; however, 1 female animal died following treatment with warfarin. Additionally, there was no elacestrant-related clinical sign or effect on body weights or food consumption during the study.

Table 8: Summary of Effects of Elacestrant on Cutaneous Bleeding Time (Report 14RAD009)

Treatment (vehicle)	Dose (mg/kg/day)	Bleeding time (minutes)		Ratio of test article to vehicle (fold)[a]	
		Male (n = 5/group)	Female (n = 5/group)	Male (n = 5/group)	Female (n = 5/group)
Vehicle (0.5% CMC)	0	8.0 ± 2.4	7.2 ± 3.0	-	-
Elacestrant (0.5% CMC)	20	8.8 ± 7.6	14.0 ± 9.1	1.1	1.9
	50	14.4 ± 12.8	10.8 ± 5.4	1.8	1.5
Warfarin (0.5% CMC)	0.25	36.8 ± 26.3	23.5 ± 24.5	4.6	3.3

- = not reported/not applicable; SD = standard deviation. [a]Values for ratio of test article to vehicle were hand calculated and not included in the study report. Data presented as mean ± SD. Source: Report 14RAD009

Wound healing

In study 14RAD30 (GLP) a potential effect of elacestrant on wound healing was addressed. Eighty male and female Sprague-Dawley rats (3 to 4 animals/sex/group) were assigned to treatment groups. Prior to dosing, 2 full thickness linear skin wounds of 2 cm were created using a scalpel and then closed using wound clips. Before dosing and on dosing days (Days 2, 3, 4, 7, 14, 21, and 28), the areas surrounding the wounds were observed and scored according to Draize. Other parameters and endpoints evaluated in this study included clinical signs, body weights, body weight changes, food consumption, ophthalmology, clinical pathology parameters (haematology, coagulation, clinical chemistry, and urinalysis), gross necropsy findings, organ weights, and histopathologic examinations.

Elacestrant was well tolerated at all dose levels. There were no mortalities and no elacestrant-related clinical signs or effects on body weight, food consumption, ophthalmology, haematology, clinical chemistry, or urinalysis.

There was an increase in fibrinogen on Day 7 (1.2×) at the ≥ 0.25 mg/kg/day dose in females and the 50 mg/kg/day dose in males. This increase was also present on Day 15 (1.1× to 1.2×) at the ≥ 0.25 mg/kg/day dose in both males and females. No fibrinogen level changes were evident on Days 22 and 29.

QD oral administration of elacestrant was well tolerated at doses up to 50 mg/kg. No significant differences between elacestrant treatment and vehicle control animals in wound healing were observed.

Gastrointestinal effects

The effect of elacestrant on gastrointestinal organs was evaluated in ferrets in 3 studies by analysing the emetic potential of elacestrant after administration (15RAD250, 16RAD223, and 16RAD231). In study 15RAD250, 24 male ferrets were assigned to treatment and morbidity/mortality checks were performed twice daily. There were no mortalities reported during the course of the study. The most common clinical observations noted across all groups were low food consumption, unformed faeces, and decreased amount of faeces. The majority of the animals experienced a general increase in body weight throughout the study, whereas animals in the 100 mg/kg group lost between 18% and 22% of

their body weight. It was shown that animals that received elacestrant at 30 and 100 mg/kg had signs of emesis, which occurred at a higher frequency in the 100 mg/kg group. In animals that received 30 mg/kg, the number of emesis observations decreased over the course of the study.

In study 16RAD223, male ferrets were assigned to treatment groups and morbidity/mortality checks were performed twice daily. All animals appeared healthy throughout the study with occasional low food consumption in all groups; there were no elacestrant-related effects on body weight. On Day 7, 1 animal that received oral elacestrant was found dead with red nasal and oral discharge. A necropsy was performed but revealed no insight to explain the discharges.

Animals that received oral elacestrant had signs of emesis (retching and vomiting). These animals retched up to 37 minutes and were observed to have retched up to 159 times during in-life. Animals that received the elacestrant free base formulation had a higher frequency of emetic events than animals that received the elacestrant salt formulations (with and without pH adjustment). The number of emesis observations decreased over the duration of the study. No emesis was observed following subcutaneous administration of 10 mg/kg elacestrant. It was shown that animals that received oral elacestrant were observed to have signs of emesis. This occurred at a higher frequency in animals that received the elacestrant free base formulation than in animals that received the elacestrant salt formulations.

In study 16RAD231, 28 male ferrets were assigned to treatment group. Morbidity/mortality checks were performed twice daily. It was shown that animals that received oral elacestrant were observed to have non-dose-related signs of emesis, which occurred more frequently in animals that received the tablet with polymer film in comparison to those that received the table with enteric coating. For most of the animals, emesis peaked on Day 3.

The most common clinical observations noted across all groups were low food consumption, vomitus, unformed faeces, and decreased amount of faeces. Animals that received elacestrant at higher doses experienced a higher frequency of emetic events (retching and vomiting).

2.5.2.4. Pharmacodynamic drug interactions

Except for the studies in combination with palbociclib and everolimus, no pharmacodynamic drug interaction studies with elacestrant have been submitted.

2.5.3. Pharmacokinetics

The effect of elacestrant on permeability and transporters (Caco-2 cells), plasma-protein binding (rat, monkey, human), metabolism and metabolite identification (rat, monkey and human hepatocytes) were studied *in vitro*. Furthermore, several PK interactions, such as cytochrome P450 induction/inhibition were also studied *in vitro*. The pharmaco- and toxicokinetic effects of elacestrant were studied *in vivo.* Several single-dose pharmacokinetic studies were performed in rats (Sprague-Dawley and Long Evans) and cynomolgus monkeys after intravenous, oral and subcutaneous dosing. Repeat-dose toxicokinetics after oral administration were studied in mice (athymic nude-Foxn1nu), rats (Sprague-Dawley and Long Evans) and cynomolgus monkeys for durations up to 39 weeks. Distribution in pregnant animals was not studied, but toxicokinetic data was collected for pregnant rats. Distribution, metabolism and excretion were not studied in the monkey.

Single- and repeat-dose kinetics

The PK of elacestrant was studied in single-dose studies in rats and monkeys. In the single-dose studies oral, IV and SC doses were investigated. Bioavailability was assessed after single-dose

administration and was dose dependent. Based on the urinary and biliary excretions in bile-duct cannulated rats, approximately 50% of a radiolabelled dose (30 mg/kg) was absorbed. However, in other studies, comparing IV versus oral administration at doses of 1, 3 and 10 mg/kg, the bioavailability was lower at about 14-23% in rats and 7.6-18.1% in monkeys (administered the same doses as the rats). The bioavailability increased with increase in dose resulting in a more than dose proportional increase in Cmax and AUC. However, at much higher doses (100-900 mg/kg), the increase was less than dose proportional, indicating a limit to the increase in bioavailability or potentially even a decrease.

It should also be noted that with increasing dose, the Tmax increases from about 2-4 hours in low doses to 8-24 hours after high doses in rats. For monkeys there is a similar effect with Tmax of 1-4 hours at low doses and 7-12 hours at higher doses. The T1/2 ranged from approximately 6 hours in rats to 11-13 hours in monkeys. Exceptions were the IV dose in monkeys (half-life approx. 4 hours) and the SC dose in rats (half-life approx. 17 hours). Volume of distribution and clearance were comparable between monkeys and rats, with Vd values of 24 and 19 L/kg and Cl values of 1.5 and 2.1 L/h/kg, respectively.

Repeat-dose studies were performed in mice, rats and monkeys. In mice doses from 30-120 mg/kg were tested. Exposure to elacestrant increased with the increase in dose level from 3 to 60 mg/kg/dose (once daily) and from 15 to 30 mg/kg/dose (BID). Generally, the increases in elacestrant Cmax, AUC0-12, and AUC0-24 values were approximately dose proportional from 3 to 15 mg/kg/dose and greater than dose proportional from 15 to 60 mg/kg/dose. A 4-fold increase in dose (from 15 to 60 mg/kg once daily) resulted in a 9.3-fold increase in Cmax and a 7.8-fold increase in AUC0-24. Half-life was stable at about 5 hours and Tmax ranged from 2-6 hours, without substantial differences between day 1 and day 7.

After repeat-dosing in rats, plasma exposure of elacestrant generally increased with increasing dose from 100 to 900 mg/kg on Day 1 and from 100 to 300 mg/kg on Day 7, and these increases were less than dose proportional. After oral administration, Tmax values ranged from 8.00 to 24.0 hours (Day 1) and from 2.00 to 8.00 hours (Day 7). The increases in exposure on Days 1 and 7 were consistently less than dose proportional, with dose increases of 3- and 9-fold (Day 1 only) producing ≤2.2-fold increases in Cmax and AUC0-24. Values for Cmax and AUC0-24 were consistently higher after 7 days of repeat dosing, but increases were not marked (i.e., remained < 2.0-fold), indicating slight/minimal accumulation. Exposure to elacestrant, as assessed by Cmax and AUC0-24, increased with the increase in dose level from 10 to 50 mg/kg/day in the 178 day study. The increases in sex-combined Cmax and AUC0-24 were approximately dose proportional on Day 1, Day 88, and Day 178. However, female rats generally exhibited higher exposure than males, with approximately 2.1-fold differences observed in Cmax and AUC0-24 on Day 88 and Day 178 in rats administered 50 mg/kg/day. The Cmax and AUC0-24 values were generally higher on Day 88 and Day 178 than on Day 1. Accumulation ratios for Cmax and AUC0-24 ranged from 0.722 to 3.47 and were higher in females than in males. In the 90-day study females had higher Cmax and AUC0-24 values than males, although no marked (> 2-fold) sex differences were observed.

In monkeys (administered 10-100 mg/kg per day) this effect was less pronounced. No accumulation of elacestrant was observed after multiple dosing in monkeys (mean accumulation ratios at Day 89 and Day 270 ranged from 0.861 to 1.69 for Cmax and from 1.05 to 1.62 for AUC0-24). The increases in mean Cmax and AUC0-24 were approximately dose proportional, except for mean AUC0-24 values for males. Mean AUC0-24 for males increased in a greater than dose-proportional manner from 20 to 30 mg/kg/day; a 3-fold increase in dose from 10 to 30 mg/kg/day resulted in 4.7- and 5.3-fold increase in AUC0-24. No marked (> 2-fold) sex differences were observed in elacestrant mean Cmax and AUC0-24 values.

Pharmacokinetic data obtained from pregnant rats (GD6 and GD17) at doses of 3-30 mg/kg per day revealed no substantial differences compared to data from non-pregnant rats at similar doses. AUC and Cmax were only marginally lower in pregnant compared to non-pregnant rats and the Tmax (4-8 hours) was a little higher compared to the non-pregnant animals (2-6 hours) at comparable dose levels. Exposure, as assessed by elacestrant Cmax and AUC0-24, increased with the increase in dose level from 3 to 30 mg/kg/day in a greater than dose-proportional manner. The 10-fold increase in dose level resulted in 22.7- to 27.2-fold increases in AUC0-24 and 18.7- and 22.7-fold increases in Cmax. Some accumulation of elacestrant was observed after multiple doses in pregnant rats, with accumulation ratios on GD 17 of 1.36 to 1.90 for Cmax and 1.55 to 2.04 for AUC0-24.

Distribution

Plasma protein binding was assessed by equilibrium dialysis and, due to the high protein binding, by the ultracentrifugation method in the range of 0.2-20 uM. This correlates to 106-10600 ng/mL (MW elacestrant 2HCl: 531.56 g/mol). The observed C_{max} values in PK and TK studies in rat and monkey are within this range. For humans the C_{max} after 400 mg PO was approx. 30-60 ng/mL depending on a fed or fasted state. Results showed that elacestrant was highly bound to the proteins in rat, monkey, and human plasma (approximately 99% binding). The percent unbound values were similar across the species, being 1.61%, 0.918% and 1.00% in rat, monkey and human plasma respectively, and did not show the concentration dependence over the tested concentration range. Although the percentage unbound elacestrant was low in all species, it should be noted that the percentage was > 1.5 fold higher in rats than in monkeys and humans.

A tissue distribution study was carried out in nonpigmented Sprague Dawley and partially pigmented Long Evans rats using ^{14}C-elacestrant. After a single oral dose of 30 mg/kg radiolabelled elacestrant, tissue distribution was widespread. Tissues with the highest exposures of radioactivity were the exorbital lacrimal gland, adrenal gland, liver, spleen, and intra-orbital lacrimal gland. Radioactivity was not measurable in the brain, eye lens, spinal cord, and testes. Tissue:plasma concentration ratios were generally >1 both in SD and LE rats, suggesting that ^{14}C-elacestrant–derived radioactivity distributed to tissues more than in plasma. ^{14}C-elacestrant-derived radioactivity in partially pigmented rats was associated with ocular melanin in the uveal tract of the eye, but was not preferentially associated with pigmented skin. Radioactivity levels in the uveal tract decreased over time, suggesting the association with ocular melanin was temporary.

In SD rats, the mean blood:plasma radioactivity concentration ratios ranged from 0.933 to 1.29 in males and 0.899 to 1.55 in females. In LE rats individual blood:plasma radioactivity concentration ratios at 0.5 through 72 hours ranged from 0.790 to 1.47. Blood:plasma ratios were not assessed for monkeys. However, no haemotoxicity was observed in single- and repeat-dose toxicity studies.

Placental transfer and excretion in milk were not assessed for elacestrant.

Metabolism

Elacestrant was extensively metabolized *in vitro* in rat (<25% parent remaining) and monkey (<33% parent remaining) hepatocytes with less extensive metabolism in human hepatocytes (approximately 40%-50% parent remaining) after 120 minutes of incubation. N-dealkylation and glucuronidation were common metabolic pathways in all species tested, producing metabolites M1, M8, M10, M13, and M15 in all 3 species. O-demethylation was specific to rat, and Phase II conjugation was more extensive in rat than monkey or human hepatocytes. Phase II metabolites M3, M4, M6, and M11 were exclusive to rat hepatocyte incubations, and sulfonation of elacestrant or metabolites was limited in monkey hepatocytes and notably absent in human hepatocytes. No unique human metabolites were observed, nor metabolites only formed in monkeys and humans. *In vivo* biotransformation was only assessed in rats. ^{14}C-elacestrant–derived components were quantified and identified/characterized in plasma,

urine, bile, and faeces from intact or bile duct–cannulated male and female Sprague Dawley rats after a single 30 mg/kg-oral dose of ^{14}C-elacestrant 2HCl. Elacestrant was extensively metabolized in rats after oral administration to yield 53 metabolites, of which 26 were identified/characterized. Primary metabolism was mediated by oxidative O-demethylation, oxidative N-dealkylation, glucuronidation, and, to a lesser extent, dehydrogenation and oxidation. Secondary oxidative N-dealkylation and glucuronidation were substantial, while secondary sulfonation, methylation, oxidation, and dehydrogenation were observed to a relatively low level.

Elacestrant and 5 metabolites were quantified and identified/characterized in rat plasma across sexes. The identified/characterized metabolites included EAEBA (M1), EAEBA glucuronide conjugates M16 and M20, methoxy elacestrant (M49), and desmethyl elacestrant glucuronide (M27). One additional metabolite, M57, was quantified in plasma from both sexes, but no structural information could be elucidated for this metabolite. Eight metabolites were quantified and identified/characterized in male rat bile. Identified/characterized metabolites included primary elacestrant glucuronide and elacestrant carbamoyl-glucuronide conjugates M8 and M53, respectively, desmethyl elacestrant glucuronide (M4), desethyl elacestrant glucuronide (M13), desmethyl desethyl elacestrant glucuronide conjugates M41 and M48, desmethyl methoxy elacestrant glucuronide (M37), and desmethyl elacestrant sulphate conjugate M45. Three metabolites were quantified and identified/characterized in rat urine across sexes and groups. Identified/characterized metabolites included EAEBA (M1), EAEBA glucuronide (M21), and EAEBA glucuronyl glutathione conjugate (M23). In addition, 5 trace metabolites (< 1% of dose), including M17, M19, M22, M25, and M36, were quantified in urine but were below the limit for structural elucidation. Elacestrant and 12 metabolites were quantified and identified/characterized in rat faeces across sexes and groups. Identified/characterized metabolites included EAEBA (M1), dehydro-elacestrant (M12), desmethyl elacestrant (M38), desmethyl elacestrant sulphate (M42), desmethyl oxy elacestrant (M30 and M33), desmethyl oxydehydro-elacestrant (M31), desethyl elacestrant (M15), desethyl oxydehydro-elacestrant (M56), desethyl methyl elacestrant (M51), and desmethyl desethyl elacestrant (M34 and M52). In addition, 7 trace to minor metabolites (M40, M54, M58, M59, M60, M61, and M62) were quantified, but no structural information was elucidated.

Metabolite M1 was a major metabolite *in vivo* in male rats (28.1%), but not in female rats (8.85%). The metabolite M1 was also seen *in vitro* in monkey hepatocytes and both *in vitro* and *in vivo* in humans (but M1 was not a major metabolite). No unique human metabolites were observed *in vitro*. In clinical human studies, the main metabolite in plasma was M16 (41.3%, a glucoronidation of M1) and the parent elacestrant was only 5.2%. In rat plasma, M16 accounted for 7.3% in males and 5.4% in females.

Excretion

As is the case with distribution and metabolism, the excretion was only assessed in rats. In both intact and bile-duct cannulated rats ^{14}C-elacestrant–related radioactivity was eliminated mainly via biliary and faecal excretion. Urinary excretion was a minor route of elimination. Urinary and faecal radioactivity accounted for 10.8% and 83.1%, respectively, of the radioactive dose in males and 2.94% and 92.5%, respectively, of the radioactive dose in females, with overall male and female means of 6.87% and 87.8% of dose, respectively. Total mean recoveries of radioactivity in males and females were 95.0% and 96.0%. Urinary, biliary, and faecal radioactivity accounted for 4.38%, 45.3%, and 47.7%, respectively, of the radioactive dose in bile duct cannulated males. The total mean recovery of radioactivity was 98.1%.

Elacestrant parent form was quantified in faeces, but not in urine, and accounted for 42.9% of dose from males and 38.7% of dose from females. EAEBA glucuronyl glutathione conjugate (M23) was the most abundant metabolite in urine from both sexes and accounted for 6.93% of dose in males and for 1.62% of dose in females, with an overall male and female mean of 4.28% of dose. In faeces, EAEBA

(M1), desmethyl elacestrant (M38), and co-eluting metabolites desethyl oxydehydro-elacestrant/desethyl elacestrant (M56/M15) were the most abundant metabolites in both sexes.

In bile duct-cannulated male rats elacestrant parent form was quantified in faeces, accounting for 48.5% of dose, but was not detected in urine and bile. Metabolites were excreted primarily in bile (36.6% of dose) and to a lesser extent in urine (3.99% of dose) and faeces (3.60% of dose). EAEBA glucuronyl glutathione conjugate M23 was the most abundant, albeit minor, metabolite in urine and accounted for 2.79% of dose. In faeces, EAEBA (M1), desmethyl elacestrant (M38), and dehydro elacestrant (M12) were trace metabolites that accounted for less than 1% of dose.

In healthy male volunteers excretion was assessed after a single-dose of 400 mg radiolabelled elacestrant (RAD1901-111). The overall mean recovery of radioactivity in urine and faeces samples was 89% over the 480-hour study, with observed mean recovery in urine and faeces of 7.53% and 81.5%, respectively, indicating that faecal excretion was the predominant route of elimination for elacestrant. The geometric mean percent of RAD1901 recovered in urine was 0.042% suggesting low renal clearance. Geometric mean values for AUC0-tlast and AUC0-∞ for elacestrant in plasma were approximately 3% and 2%, respectively, of those for total radioactivity in plasma suggesting the presence of circulating metabolites.

Compared to the recovery of radiolabelled elacestrant in rats, the excretion in humans appears to be similar, with the faeces as the predominant route of elimination, low recovery in urine, presence of circulating metabolites and only a very low clearance of parent elacestrant in urine.

Pharmacokinetic drug interactions

Studies in human liver microsomes and with recombinant enzymes revealed that elacestrant was a substrate of CYP3A4 with a minor contribution of CYP2A6 and CYP2C9. No reaction phenotyping studies for UGTs were submitted.

In vitro studies assessing possible relevance of metabolic enzymes for drug interactions of elacestrant are summarised in Table 9.

Table 9: Overview of *in vitro* studies assessing relevance of metabolic enzymes for drug interactions of elacestrant.

Elacestrant:	Study system	Enzymes	Results / IC_{50} or K_i	Implications
inhibitor	human liver microsomes	CYP1A2	no inhibition up to 30 μM	no in vivo study needed* if $IC_{50} = K_i$
		CYP2A6	IC_{50} = 29 μM	
		CYP2B6	no inhibition up to 30 μM	
		CYP2C8	IC_{50} = 4.1 μM	
		CYP2C9	IC_{50} = 11.6 μM	
		CYP2C19	IC_{50} = 13.2 μM	
		CYP2D6	IC_{50} = 27.1 μM	

		CYP2E1	no inhibition up to 30 μM	
		CYP3A4/5 (midazolam)	IC_{50} = 25.9 μM	no inhibition if $IC_{50} = K_i$
		CYP3A4/5 (testosterone)	IC_{50} = 15.3 μM	
inhibitor, time-dependent	human liver microsomes	CYP2A6	no effect of NADPH pre-incubation	no irreversible inhibition
		CYP2B6		
		CYP2C8		
		CYP2C19		
		CYP3A4/5		
inducer[#]	human hepatocytes	CYP1A2	no changes in activity	no induction
		CYP2A6	activity reduction by 62-100% in 3/4 donors	
		CYP2B6	activity reduction by 32% in 2/4 donors	
		CYP2C9	activity reduction by 100% in 1/4 donors	
		CYP2C19	activity reduction by 57-100% in 4/4 donors	
		CYP3A	activity reduction by 86-100% in 4/4 donors	

[*]need for in vivo study as estimated by the assessor according to the EMA guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**): in vivo evaluation is warranted if $[I]/K_i \geq 0.02$ where [I] is the unbound mean C_{max} obtained during treatment with the highest recommended dose, for CYP3A4 also if $[I]/K_i \geq 10$ where [I] is the maximum dose on one occasion/250 ml

[#]induction was considered present if fold change in mRNA level was > 2

Data from an evaluation of enzyme induction (CYP1A2, CYP2B6 and CYP3A4) in cryopreserved human hepatocytes in a collagen-sandwich configuration on the mRNA level were also presented. Cytotoxicity was shown by LDH release at concentrations above 10 μM. Therefore, only concentrations up to 3 μM were analysed for mRNA induction. Respecting the nominal free concentration after correction for protein binding in incubation medium, the three analysed doses (0.3, 1 and 3 μM) were in the recommended range for analysis as 3 μM were above a 50-fold $C_{max.u}$ at the maximum recommended daily dose of 345 mg elacestrant. Enzyme induction was in general low for all 3 enzymes and below 100% induction (2-fold) except for CYP1A2 in one donor. EC_{50} and E_{max} were not determined due to the high variability. Irrespective if the increase in CYP1A2 mRNA induction was concentration dependent for the analysed range of 0.3 up to 3 μM, the observed increase represented only 3% of the prototype inducer omeprazole and was therefore below the cut off (20% of model inducer) for an inducer according to CPMP/EWP/560/95/Rev. 1 Corr. 2**. CYP2C enzymes were not further analysed due to negative results for CYP3A4 mRNA induction and the fact that both enzymes share the same signalling pathway (PXR) for induction.

In vitro studies assessing possible relevance of transport proteins for drug interactions of elacestrant are summarised in Table 10.

Table 10: Overview of *in vitro* studies assessing relevance of transporters for drug interactions of elacestrant.

Elacestrant:	Study system	Transporters	Results / unbound IC_{50} or K_i	Implications
substrate	HEK293 cells overexpressing transporters	OATP1B1/3	no difference in uptake between transfected and control cells	elacestrant – not a substrate
		OCT1/2		
		OAT1/3		
		MATE1		
		MATE2-K	>2-fold increase in uptake vs control, not affected by specific inhibitor	
		OATP2B1	2.6-fold increase in uptake vs control, affected by specific inhibitor	elacestrant – a transporter substrate
inhibitor	HEK293 cells overexpressing transporters	MATE1	IC_{50} = 15.9 μM	no in vivo study needed*
		MATE2-K	IC_{50} > 50 μM	
		OAT1/3		
		OCT2		
		OATP1B1		
		OATP1B3	IC_{50} > 5 μM	
		OCT1	IC_{50} = 1.72 μM	
		BCRP	IC_{50} = 44.1 μM	in vivo study warranted*
		P-gp	IC_{50} = 7.0 μM	

*need for in vivo study as estimated by the assessor according to the EMA guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**): in vivo evaluation is warranted if K_i ≤

- for intestinally expressed transporters: 0.1-fold the maximum dose on one occasion/250 ml
- for hepatic uptake transporters: 25-fold the unbound hepatic inlet concentration
- for renal uptake and efflux transporters, for hepatic efflux transporters: 50-fold unbound C_{max}

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Several single-dose oral toxicity studies with elacestrant have been conducted in female Sprague Dawley (SD) rats at doses up to 1200 mg/kg and in female Cynomolgus monkeys at doses up to 500 mg/kg.

Table 11: Single dose toxicity studies in rats conducted with elacestrant

Study ID	**Species** Nr/Sex/Group	**Dose** (mg/kg) **Route/Vehicle**	**Major findings**
7801-111 Non-GLP	SD rats 3 F/group	30, 100, 300, 600, 1200, 900 Oral gavage 0.5% CMC-Na **MTD: 900 mg/kg**	**Mortality:** - 1x 600 mg/kg female died on day 2 (procedure-related) - 1x 1200 mg/kg female was sacrificed on day 2 (clear oral discharge, laboured respiration, piloerection, ↑ NEUT/MONO, ↓ LYMP, ↑ AST/ALT/ALP, distended stomach/small intestine, discoloration of glandular stomach - treatment-related) **Day 3 post dose:** **≥100:** ↓ ALB:GLOB ratio **≥300:** ↑ CHOL **≥600:** ↓ BW/food intake, ↑ NEUT, ↑ ALT **≥900:** clear oral discharge **=1200:** irregular respiration, unformed/no faeces
7801-113 GLP	SD rats 7 F/group + 3-12 F/ group for TK	0, 100, 600, 900 Oral gavage 0.5% CMC-Na **MTD: 900 mg/kg**	**Day 3 post dose:** **≥600:** clear/red oral discharge, unformed faeces, ↑ NEUT/MONO, ↑ ALT **=900:** ↓ BW gain/food intake **Day 15 post dose:** **≥600:** ↑ ALP, ↑ UN **=900:** ↓ GLU, ↑ AST

ALB: albumin, ALT: alanine aminotransferase, ALP: alkaline phosphatase, AST: aspartate aminotransferase, BW: bodyweight, CHOL: cholesterol, GLOB: globulin, GLU: glucose, LYMP: lymphocytes, MONO: monocytes, MTD: maximum tolerable dose, NEUT: neutrophils, UN: urea nitrogen

In a non-GLP dose range finding study in female rats, treatment-related decreases in body weight and food intake were observed at ≥ 600 mg/kg elacestrant 3 days post-dosing. Additionally, higher liver enzyme levels (alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST)) and increased white blood cell counts (neutrophils, monocytes) were observed. One high dose female rat treated with 1200 mg/kg elacestrant was sacrificed in moribund condition on day 2, and macroscopic observations included distended stomach and small intestine and discoloration of glandular stomach.

In a definitive GLP-compliant single-dose toxicity study in female rats, animals treated with ≥ 600 mg/kg elacestrant showed increased ALT levels, and increased neutrophil and monocyte counts 3 days post-dosing. Fifteen days post-dosing, these findings were resolved, although ALP levels increased between day 3 and 15 post-dosing. At 900 mg/kg, decreases in body weight gain and food intake were observed, but this was resolved at day 15 post-dosing. Therefore, the maximum tolerable dose (MTD) was considered 900 mg/kg in female rats.

Table 12: Single dose toxicity studies in monkeys conducted with elacestrant

Study ID	**Species** Nr/Sex/Group	**Dose** (mg/kg) **Route/Vehicle**	**Major findings**
7801-112 GLP	Cynomolgus monkey 2 F/group	Escalating dose: 10 (G1), 30 (G2), 100 (G1), 300 (G2), 500 (G1) Oral gavage 0.5% CMC-Na **MTD: 900 mg/kg**	**Group 1 (G1):** ≥100: ↓ food intake, unformed faeces, vomitus **Group 2 (G2):** ≥30: ↓ food intake, discoloration of the stomach =300: vomitus
7801-136 GLP	Cynomolgus monkey 3 F/group	0, 0.85 IV bolus 0.9% sterile saline	No clear treatment-related findings

MTD: maximum tolerable dose

In a GLP-compliant escalating single-dose toxicity study in female monkeys, animals treated with ≥ 30 mg/kg had decreased food intake. At ≥ 100 mg/kg, adverse effects included vomitus and unformed faeces. Macroscopic observations revealed discoloration of the stomach in one female treated with 30 and 300 mg/kg. The MTD was considered 500 mg/kg in female monkeys.

An additional GLP-compliant study with IV bolus administration of 0.85 mg/kg elacestrant in female monkeys did not show any clear treatment-related findings.

2.5.4.2. Repeat dose toxicity

Several repeat-dose oral toxicity studies with elacestrant have been conducted in SD rats at doses up to 900 mg/kg for up to 26 weeks, and in Cynomolgus monkeys at doses up to 1000 mg/kg for up to 39 weeks. Initial studies were only performed in female animals, but later studies were conducted in both sexes.

Table 13: Repeat-dose toxicity studies in rats conducted with elacestrant

Study ID	**Species** Nr/Sex/Group	**Dose** (mg/kg/day) **Route/Veh.**	**Duration**	**Major findings**
7801-111 Non-GLP	SD rats 5 F/group + 3-9 F/group for TK	0, 100, 300, 900 Oral gavage 0.5% CMC-Na **NOAEL: 100 mg/kg/day**	7 days	**Mortality:** - 2x 900 mg/kg/day females were found dead on day 3. - All remaining animals in the 900 mg/kg/day group were sacrificed on day 3 due to rapidly declining health (hypoactivity, swollen abdomen, clear oral/nasal discharge, irregular respiration, few/unformed faeces, ↑ RBC/HGB/HCT, ↑ PLAT/NEUT/MONO, ↓ LYMP/EOS, ↑ GLU/UN/CREAT, ↑ TPRO/GLOB, ↓ ALB:GLOB ratio, ↑ AST/ALT/GGT, distended stomach, discoloration of the non-glandular/glandular stomach - treatment-related) **≥100:** ↑ PLAT/WBC/NEUT/MONO, ↓ TPRO/ALB, ↓ ALB:GLOB ratio **=300:** clear oral discharge, unformed faeces, audible respiration, ↓ BW/food intake, ↑ RBC/HGB/HCT, ↓ RET/LYMP, ↑ UN, ↓ CHOL, ↑ AST/ALT, ↓ ALP

Study ID	**Species** Nr/Sex/Group	**Dose** (mg/kg/day) **Route/Veh.**	**Duration**	**Major findings**
7801-114 GLP	SD rats 10-15 F/group + 3-12 F/group for TK + 5 F/ group for recovery	0, 20, 50, 120 Oral gavage 0.5% CMC-Na **NOAEL: not determined**	28 days + 14 days recovery	**Mortality:** - 1x control female died on day 30 (procedure-related) - 1x 120 mg/kg/day female died on day 26 (thin appearance, few faeces, laboured respiration. Necropsy not performed - death is likely treatment-related) **Main phase:** **≥20:** ↑ RBC/HGB/HCT, ↑ AST/ALT/ALP, ↓ pituitary gland/uterus weight, ↑ ovary weight, luteal hypertrophy, luteal cysts in ovary, uterus/cervix atrophy **=120:** clear oral discharge, red nasal discharge, few faeces, irregular respiration, squinted eyes, thin appearance, ↓ food intake, ↑ RET/WBC/NEUT/MONO, ↓ TPRO/ALB, ↓ ALB:GLOB ratio, ↑ liver/lung weight, ↓ thymus weight, vacuolization in marginal zone of splenic follicles, histiocytic infiltrate in mesenteric lymph node, foamy macrophages in lamina propria of small intestine, lesions in mucosa of the small intestine, chronic active inflammation of the mucosa **Recovery phase (control and high dose only):** **=120:** ↑ BW/food intake, ↑ RBC/HGB/HCT, ↓ RET, ↓ TPRO/ALB, ↓ CHOL, ↑ ALP, ↑ ovary weight, luteal hypertrophy, luteal cysts in ovary, uterus atrophy
16RAD206 GLP	SD rats 10/sex/group + 3-6/sex/group for TK	0, 20, 50, 120 Oral gavage 0.5% CMC-Na **NOAEL: not determined**	28 days	**Mortality:** - 2x 120 mg/kg/day female were sacrificed on day 15 and 18 (hypoactivity, irregular/audible/laboured respiration - treatment-related) - 1x 120 mg/kg/day male was found dead on day 25 (cause unknown, but similar microscopic findings as other high dose animals - treatment-related) **≥20:** ↓ BW/food intake (M), ↓ RET (M), ↓ TPRO/ALB (F), ↓ ALB:GLOB ratio (F), ↓ CHOL/GLU, ↓ TRIG (M), ↑ ALP/ALT/AST (F), ↑ ovary weight, ↓ uterus weight, ↓ pituitary weight, cysts in ovary, uterus atrophy, vacuolated macrophages in small intestine (F), tingible-body macrophages in thymus **≥50:** bile duct epithelium vacuolation in liver (F) **=120:** ↓ BW/food intake (F), ↑ WBC/NEUT/MONO, ↑ LYMP (M), ↓ TPRO/ALB (M), ↓ ALB/GLOB ratio (M), ↓ UN (F), ↓ thymus weight, bile duct epithelium vacuolation in liver (M), vacuolated macrophages in small intestine (M)

Study ID	Species Nr/Sex/Group	Dose (mg/kg/day) Route/Veh.	Duration	Major findings
7801-130 GLP	SD rats 10-15/sex/ group + 3-9/ sex/group for TK + 5/sex/ group for recovery	0, 20, 50, 100 Oral gavage 0.5% CMC-Na **NOAEL: not determined**	13 weeks + 4 weeks recovery	**Mortality:** - 1x 100 mg/kg/day female died on day 1 (procedure-related) - 4x 100 mg/kg/day males were sacrificed on day 23, 35 and 87 (hunched posture, abnormal breathing, abnormal faeces, oral discharge – treatment-related) - 2x 100 mg/kg/day females were sacrificed on day 69 and 83 (hunched posture, abnormal breathing, abnormal faeces, oral discharge – treatment-related) **Main phase:** **≥20:** few/unformed faeces, ↓ BW/food intake (M), ↑ RBC/HCT (F), ↓ CHOL, ↑ ALP, ↑ ovary weight, ↓ uterus weight, ↓ pituitary weight, male mammary differentiation (F), cysts in ovary, uterus/cervix/vagina atrophy **≥50:** laboured/irregular breathing, ↑ ALT (M) **=100:** clear oral discharge, ↑ PLAT/WBC/NEUT/MONO, ↓ ALB, ↓ ALB:GLOB ratio, ↑ AST, ↓ thymus weight (M), vacuolation in marginal zone of splenic follicles (F), foamy macrophage infiltrate in marginal zone of splenic follicles, foamy macrophage/histiocytic infiltrate in lamina propria of small intestine/mesenteric lymph node, mineralization of the kidney **Recovery phase (control and high dose only):** **=100:** ↓ BW (M), ↑ ovary weight, ↓ pituitary weight (F), cysts in ovary, mineralization of the kidney

Study ID	Species Nr/Sex/Group	Dose (mg/kg/day) **Route/Veh.**	Duration	Major findings
15RAD215GLP	SD rats 10-15/sex/group + 3-9/sex/group for TK + 5/sex/group for recovery	0, 10, 25, 50 Oral gavage 0.5% CMC-Na **NOAEL: not determined**	26 weeks + 4 weeks recovery	**Mortality:** - 1x control male was sacrificed on day 151 (laboured breathing, lateral recumbence, haemorrhage of brainstem – not treatment-related) - 2x 10 mg/kg/day females died on day 88 (procedure-related) - 1x 10 mg/kg/day male was sacrificed on day 170 (severe haemorrhage into the bladder, suspected to be caused by cystitis, glomerulonephritis, or another unidentified reason – not treatment-related) - 1x 25 mg/kg/day male was sacrificed on day 178 (head tilt, hypoactivity, laboured breathing - cause unknown) **Main phase:** **≥10:** ↓ BW/food intake (M), ↑ RBC/HGB/HCT (F), ↓ RET (M), ↓ PLAT, ↓ TPRO/ALB (F), ↓ ALB:GLOB ratio (F), ↑ ALP (F), ↓ CHOL, ↑ ovary weight, granulosa cell hyperplasia and follicular cysts in ovary, ↓ uterus/pituitary weight, uterus/cervix/vagina atrophy, ↑ kidney weight (M), decreased corpora lutea, increased trabecular bone in femur (M), decreased number and increased thickness of trabecular bone in femur (F), mineralization of the kidney **≥25:** excessive salivation, granulosa cell neoplasms in ovary, alveolar hypertrophy/hyperplasia of the mammary gland (F), vacuolation of mucosal epithelium in non-glandular stomach, increased granulocytes in glandular stomach **=50:** clear oral discharge, ↑ NEUT (F), luteoma in ovary, decreased cellularity of interstitial/Leydig cells in testis, lymphoid follicles/macrophage aggregates in mesenteric lymph nodes **Recovery phase (control and high dose only):** **=50:** ↑ ovary weight, granulosa cell neoplasm and follicular cysts in ovary, ↓ uterus/pituitary weight, uterus atrophy, ↑ kidney weight (M), increased trabecular bone in femur (M), decreased number and increased thickness of trabecular bone in femur (F), lymphoid follicles/macrophage aggregates in mesenteric lymph nodes, mineralization of the kidney (M)

ALB: albumin, ALT: alanine aminotransferase, ALP: alkaline phosphatase, AST: aspartate aminotransferase, BW: body weight, CREAT: creatinine, EOS: eosinophils, GGT: gamma glutamyl transferase, GLOB: globulin, GLU: glucose, HCT: haematocrit, HGB: hemoglobulin, LYMP: lymphocytes, MONO: monocytes, NEUT: neutrophils, PLAT: platelets, RBC: red blood cells, RET: reticulocytes, TPRO: total protein, TRIG: triglycerides, UN: urea nitrogen, WBC: white blood cells

Table 14: Repeat-dose toxicity studies in monkeys conducted with elacestrant

Study ID	**Species** Nr/Sex/Group	**Dose** (mg/kg/day) **Route/Veh.**	**Duration**	**Major findings**
7801-112 GLP	Cynomolgus monkey 2 F/group	0, 50, 200, 1000 Oral gavage 0.5% CMC-Na **NOAEL: not determined**	7 days	**Mortality:** Both 1000 mg/kg/day females were sacrificed on day 2 (dehydration, hypoactivity, lateral recumbence, vomitus, excessive salivation, liquid faeces, ↓ food intake, ↑ RBC/HGB/HCT, ↑ WBC/NEUT/MONO, ↓ LYMP/EOS, ↑ GLU/UN/CREAT, discoloration/ thickening of stomach/cecum – treatment-related) **≥50:** vomitus, ↓ food intake, ↑ ALT **=200:** liquid/unformed faeces, ↓ BW, ↑ GLU
7801-115 GLP	Cynomolgus monkey 3/F/group + 2 F/group for recovery period	0, 20, 50, 100 Oral gavage 0.5% CMC-Na **NOAEL: not determined**	28 days + 14 days (control) or 28 days (high dose) recovery	**Mortality:** - 1x 50 mg/kg/day female was sacrificed on day 27 (hypoactivity, liquid/unformed faeces, cold to touch, ↓ BW/food intake, acute inflammation in stomach – cause unknown, but treatment-related) - 3x 100 mg/kg/day females were sacrificed on day 13 (1x) and day 15 (2x) (dehydration, hypoactivity, vomitus, excessive salivation, liquid/unformed faeces, ↓ BW/food intake - cause unknown, but treatment-related. Vasculitis/perivasculitis in kidney/liver/ gallbladder/colon/cecum/rectum was observed in 1 animal sacrificed on day 15. Acute inflammation in stomach was observed in 1 other animal) Dosing stopped in the surviving 100 mg/kg/day females on day 15, and they remained in the recovery phase for 28 days. **Main phase:** **≥20:** vomitus, ↑ WBC/MONO/LYMPH, ↑ ovary weight, follicular cysts in ovary **≥50:** hypoactivity, liquid/unformed faeces , ↓ food intake, ↓ RBC, ↑ NEUT, ↓TPRO/ALB, ↓ CHOL, ↑ ALT, ↓ ALP/GGT **=100:** dehydration, excessive salivation, ↓ BW **Recovery phase (control and high dose only):** **=100:** ↑ ALT, ↑ ovary weight
7801-134 GLP	Cynomolgus monkey 3/sex/group + 2/sex/group for recovery period	0, 10, 20, 30 Nasogastric intubation 0.5% CMC-Na **NOAEL: not determined**	13 weeks + 4 weeks recovery	**Main phase:** **≥10:** ↑ ALT (F), ↑ ovary weight, follicular cysts in ovary, ↓ uterus weight, uterus/cervix/vagina atrophy, hypertrophy/hyperplasia in mammary gland (M) **≥20:** ↑ ALT (M) **=30:** ↓ food intake, ↓ thymus weight (M) **Recovery phase (control and high dose only):** **=30:** ↑ ovary weight, ↓ uterus weight, follicular cysts in ovary

Study ID	Species Nr/Sex/Group	Dose (mg/kg/day) Route/Veh.	Duration	Major findings
15RAD216 GLP	Cynomolgus monkey 4/sex/group + 2/sex/group for recovery	0, 10, 20, 30 Oral gavage 0.5% CMC-Na **NOAEL: not determined**	39 weeks + 4 weeks recovery	**Main phase:** **≥10:** ↑ ovary weight, ↓ uterus weight, follicular cysts and increased ovarian stroma in ovary, uterus/cervix/vagina atrophy, mammary gland atrophy (F) **≥20:** ↓ food intake (F), ↑ AST (F), basophilic pituicytes in pituitary (M), vacuolated macrophage infiltrates in small intestine **=30:** excessive salivation, ↑ ALT, ↑ pituitary weight (M) **Recovery phase (control and high dose only):** **=30:** ↑ ovary weight, increased ovarian stroma, ↓ uterus weight, mammary gland atrophy (F)

ALB: albumin, ALT: alanine aminotransferase, ALP: alkaline phosphatase, AST: aspartate aminotransferase, BW: body weight, CREAT: creatinine, EOS: eosinophils, GGT: gamma glutamyl transferase, GLU: glucose, HCT: haematocrit, HGB: hemoglobulin, LYMP: lymphocytes, MONO: monocytes, NEUT: neutrophils, RBC: red blood cells, TPRO: total protein, UN: urea nitrogen, WBC: white blood cells

2.5.4.3. Genotoxicity

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

Table 15: Overview of genotoxicity studies conducted with elacestrant

Type of test/ study ID	Test system	Concentrations/ Vehicle	Results Positive/negative/equivocal
Gene mutations in bacteria 7801-100 GLP	*S. typhimurium* (TA98, TA100, TA1535, TA1537) and *E. coli* (WP2*uvrA*)	0.5-100 µg/plate -S9 5-500 µg/plate +S9 DMSO	**Cytotoxicity:** ≥333 µg/plate in TA100 and WP2*uvrA* +S9 ≥10 µg/plate in TA100 –S9 ≥33.3 µg/plate in WP2*uvrA* -S9 Precipitation at ≥333 µg/plate **Negative for mutagenicity**
Gene mutations in bacteria 15RAD251 GLP	*S. typhimurium* (TA98, TA100, TA1535, TA1537) and *E. coli* (WP2*uvrA*)	0.5-5000 µg/plate ±S9 DMSO	**Cytotoxicity:** ≥160 µg/plate in TA100 and WP2*uvrA* +S9 ≥500 µg/plate in TA98, TA1535 and TA1537 +S9 ≥16 µg/plate in TA1537 -S9 ≥50 µg/plate in TA98, TA100 and TA1535 -S9 ≥160 µg/plate in WP2*uvrA* -S9 Precipitation at ≥1600 µg/plate **Negative for mutagenicity**
Chromosomal aberrations *in vitro* 15RAD252	Primary human lymphocytes	**Initial exp.:** 3 hours: 3.39-500 µg/ml ±S9	**Cytotoxicity:** ≥16.6 µg/ml for 3 hours -S9 ≥9.89 µg/ml for 24 hours -S9

Type of test/ study ID	Test system	Concentrations/ Vehicle	Results Positive/negative/equivocal
GLP		24 hours: 3.39-500 µg/ml -S9 **Repeated exp.:** 3 hours: 3.8-34.7 µg/ml -S9 6.43-58.8 µg/ml +S9 DMSO	≥42.3 µg/ml for 3 hours +S9 ↑ polyploidy at 39.0 and 43.2 µg/ml for 3 hours +S9 (cytotoxicity 24% and 54% respectively) **Negative for clastogenicity**
Chromosomal aberrations *in vitro* 7801-101 GLP	Cultured human lymphocytes	**Initial exp.:** 3 hours: 4.75-700 µg/ml ± S9 **Repeated exp.:** 3 hours: 2-40 µg/ml +S9 ~22 hours: 0.25-20 µg/ml -S9 DMSO	**Cytotoxicity:** ≥9.69 µg/ml for 3 hours +S9 ≥3 µg/ml for 3 hours -S9 ≥25 µg/ml for 24 hours -S9 **Negative for clastogenicity**
Chromosomal aberrations *in vivo* 7801-102 GLP	SD rats 5 F/group	0, 50, 300, 900 mg/kg/day for 2 days Oral gavage 0.5% CMC-Na	**Mortality:** - 1x 900 mg/kg/day female was found dead on day 3 (cause unknown - treatment-related) **Clinical observations:** **≥300:** clear oral discharge, hypoactivity, hunched posture, unformed/liquid faeces, audible/irregular breathing No increase in micronucleated polychromatic erythrocytes, and no bone marrow cytotoxicity **Negative for clastogenicity**

2.5.4.4. Carcinogenicity

Carcinogenicity studies were not submitted. However, granulosa ovary cell benign tumours were present in female rats following 26-week treatment with elacestrant at doses ≥25 mg/kg/day; a similar finding was described in the 2-year carcinogenicity study using fulvestrant (NDA 21-344 Pharmacology Review 2002; Faslodex EPAR 2020). Such tumours have been associated with long-term perturbation of endocrine function induced by selective oestrogen receptor modulators (SERMs), such as raloxifene, or such tumours may develop spontaneously in mice lacking ERα (Capen 2004).

2.5.4.5. Reproductive and developmental toxicity

Fertility studies were not submitted (see 2.5.6. discussion on non-clinical aspects). Adverse effects of elacestrant on both male and female fertility can be anticipated based on its mechanism of action. Fertility was reversibly impaired in female rats following treatment with fulvestrant (NDA 21-344 Pharmacology Review 2002; Faslodex EPAR 2020), bazedoxifene (NDA 022247 2013), or raloxifene

(NDA 020815 1997), whereas in male rats repeated administration of fulvestrant induced loss of spermatozoa and epididymides degeneration (NDA 21-344 Pharmacology Review 2002; Faslodex EPAR 2020). Decreased cellularity of Leydig cells was noted in male rats at the highest dose of elacestrant (50 mg/kg/day) in the 26-week repeat-dose study, and this result was in line with the impaired male (and female) fertility described in ERα knockout mice (Korach 1994).

No early embryonic development toxicity study was submitted (see 2.5.6. discussion on non-clinical aspects).

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

Table 16: Embryo-foetal developmental toxicity studies conducted with elacestrant

Study ID	**Species** (Nr/F/Group)	**Dose** (mg/kg/day)	**Dosing period**	**Major findings**
19RAD230 GLP	Sprague-Dawley rats 10/F/group + 3-9/F/group for TK	0, 0.3, 3, 10, 30 Oral gavage 0.5% CMC-Na **NOAEL: 0.3 mg/kg/day (Both F0 and F1)**	GD6-17	**F0 animals:** ≥3: red vulvar discharge, ↓ food intake, ↑ total litter loss, ↑ post-implantation loss, ↑ early/late resorptions, ↓ live foetuses ≥10: ↓ body weight, ↓ gravid uterine weight **F1 animals:** ≥0.3: visceral oedema ≥3: ↓ body weight ≥10: domed/flattened/misshapen head or micrognathia, skeletal malformations of skull, hyperflexion and malrotation of limbs

No studies to assess the effects on pre- and postnatal development, including maternal function, were submitted (see 2.5.6. discussion on non-clinical aspects).

Non-clinical studies in offspring / juvenile animals were not submitted (see 2.5.6. discussion on nonclinical aspects).

2.5.4.6. Toxicokinetic data

A substantial amount of toxicokinetic data has been collected in the pivotal animal species rat and monkey. Numerous single- and repeat dose toxicokinetic studies, with different dosages ranging from 10-900 mg/kg, were performed in rats. Because of the high protein binding, small differences in unbound fractions can be of influence for the therapeutic and toxicological effect of elacestrant. Therefore, the exposure margins were re-calculated with the AUCs corrected for the unbound elacestrant fractions. Exposure multiples from 0.49-16.73 were achieved in rats. In pregnant rats (dosed 3-30 mg/kg) exposure margins were 0.09-3.87. In monkeys both single- and repeat-dose studies were performed. The dose ranged from 10-1000 mg/kg and exposure multiples were re-calculated at 0.23-3.51.

2.5.4.7. Local Tolerance

An GLP-compliant local tolerance study was conducted in male New Zealand white rabbits (Study 7801-135), with IV and perivenous administration of elacestrant at a dose concentration of 0.2 mg/mL. No treatment-related findings occurred, and elacestrant was locally well tolerated.

2.5.4.8. Other toxicity studies

Studies on impurities: There are no mutagenic impurities in the current drug substance based on the *in silico* predictions with Derek Nexus and Leadscope software methods (Study 20RAD232, 185100B, 8379173). Two intermediates, N-(2-bromo-5-methoxyphenyl)acetamide and 2-bromo-4-methoxyaniline, were considered to be potentially mutagenic (Class 3 compound) based on structural alerts. These 2 intermediates were eliminated through the combination of in-process control and purging and are not present in the current batches of drug substance. Additionally, impurities present in clinical lots of elacestrant exceeding qualification threshold levels, per ICH Q3A (for non-oncology indications), were either considered qualified in repeat-dose toxicology studies or associated with no additional risks beyond the active pharmaceutical ingredient.

Phototoxicity: A GLP-compliant neutral red uptake phototoxicity assay in BALB/c 3T3 mouse fibroblasts was conducted with elacestrant (potential phototoxicity measured by a reduction in viability of cells pre-incubated with elacestrant at concentrations up to 31.6 µg/mL and exposed to ultraviolet radiation for approximately 30 minutes (Study 16RAD249)). The photo irritation factor was ≤ 1.118 and the mean photo effect was ≤ 0.001, indicating no phototoxic potential of elacestrant.

Other toxicity studies: No dedicated studies on antigenicity, immunotoxicity or dependence were submitted. No studies with elacestrant metabolites were submitted (see discussion on non clinical aspects).

2.5.5. Ecotoxicity/environmental risk assessment

Table 17: Summary of main study results

Substance (INN): elacestrant dihydrochloride			
CAS-number (if available): 722533-56-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD123	log D_{ow}: 1.55 (pH 5) log D_{ow}: 3.27 (pH 7) log D_{ow}: 4.77 (pH 9)	Potential PBT (Y)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	log D_{ow}: 1.55 (pH 5) log D_{ow}: 3.27 (pH 7) log D_{ow}: 4.77 (pH 9)	
	BCF	TBD	
Persistence	Ready biodegradability	TBD	
	DT50	TBD	
Toxicity	NOEC algae	TBD	

	NOEC crustacea		
	NOEC fish		
	CMR	not investigated	potentially T
PBT-statement :	The compound is potentially PBT/vPvB.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surface\ water}$, refined (prevalence), for the elacestrant ion	0.116	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)	endocrine active		(Y)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	*TBD*	List all values
Ready Biodegradability Test	OECD 301F	TBD	toxicity to micro-organisms observed at 100 mg/L. Test needs to be repeated
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	TBD	Not required if readily biodegradable DT_{50} values at 20°C; Significant shifting to sediment observed (Y/N).

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	TBD	µg/L	endpoint
Daphnia sp. Reproduction Test	OECD 211	NOEC	TBD	µg/L	endpoint
Fish, Full Life Stage Toxicity Test/*Species*	OECD 210	NOEC	TBD	µg/L	endpoint
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	TBD	µg/L	respiration
Phase IIb Studies					
Bioaccumulation/*Species*	OECD 305	BCF	TBD	L/kg	%lipids:

TBD = To be determined

Elacestrant dihydrochloride is potentially PBT/vPvB, the PBT assessment cannot be finalised in absence of the required studies.

2.5.6. Discussion on non-clinical aspects

Pharmacology

In vitro studies showing degradation of ER by increasing doses of elacestrant and fulvestrant suggest that ER degradation was more effective with fulvestrant as compared to elacestrant. This suggestion seems to be supported by the fact that the IC50 of fulvestrant for growth inhibition in MCF-7 was 0.8 nM (Nukatsuka et al, 2019 doi: 10.21873/invivo.11622). This was lower than the IC50 of elacestrant for growth inhibition in MCF-7, which was 4.2 nM with and 5.6 nM without E2, respectively. *In vitro* studies did not include any comparison to fulvestrant. *In vitro* tests suggest that elacestrant has the potential to inhibit the (E2 induced) proliferation of MCF-7 cells, of HCC1428-long-term oestradiol deprivation [LTED] cells, of ESR1 mutant-bearing MCF7-Y537S and MCF7-D538G cells and of tumour cells in a post-CDK4/6 inhibitor setting. The growth inhibitory effect observed appeared to be independent of ESR1 status (wild type or mutant) and the CDK4/6 inhibitor used to develop resistance. The comparison of elacestrant pharmacological effect on the wild-type (wt) and mutant (mt) ESR1 was especially interesting in the light of clinical efficacy data that showed a clear improvement in progression-free survival in subjects with mt-ESR1 and no clear difference compared to the standard of care in patients having wt-ESR1 (see clinical aspects). Given similar growth inhibitory effect of elacestrant in MCF-7 cells with wt- and mt-ESR1, the pharmacology behind the clinical observations is unclear. The Applicant discussed the mechanistic background of differences in clinical efficacy of elacestrant in patients featuring the wild-type and mutant ESR1, which is reflected below.

Elacestrant was evaluated for anti-tumour activity in several *in vivo* ER-positive breast cancer models. Tumour growth inhibition by elacestrant was assessed in an oestrogen responsive MCF-7 human breast carcinoma and multiple nude mouse PDX models, using cells insensitive to fulvestrant and CDK4/6 inhibitors and cells harbouring mutations in ESR1 gene. However, cells that were selected from patients because of their insensitiveness to fulvestrant or CDK4/6 inhibitors, were cultured afterwards or proliferated otherwise, which may have affected the regulation of ER and therefore also other characteristics of the model. Thus, the predictive value of the *in vivo* models for the efficacy of elacestrant in (specific) patient (populations) is limited.

In *in vivo* anti-tumour studies using a mouse xenograft model, treatment with elacestrant significantly inhibited the oestrogen-dependent growth of MCF-7 breast cancer tumours at doses of 30 mg/kg (TGI = 66% to 100.5%), 60 mg/kg (TGI = 88% to 103.4%), 90 mg/kg (TGI = 94%), and 120 mg/kg (TGI = 94% to 103.6%). However, treatment with fulvestrant and tamoxifen resulted in similar and significant anti-tumour effects. Unfortunately, the enantiomeric purity of the elacestrant test product has not been specified. Given different pharmacological activity of the R- and S-isomers, the presence of the less active S-isomer in the product could have impacted the outcome of non-clinical studies. Additionally, elacestrant was associated with prolonged survival in mice implanted with MCF-7 tumour cells intracranially, whereas fulvestrant was not. It is suggested that elacestrant passes the blood brain barrier, however, it was not shown to distribute to the brains in the distribution study.

The anti-tumour effect of elacestrant was also evaluated in multiple nude mouse PDX models, using cells insensitive to fulvestrant and CDK4/6 inhibitors and cells harbouring mutations in ESR1 gene as well as PIK3CA. Overall, elacestrant exhibited anti-tumour activity at doses of 10 mg/kg (TGI = 72% to 73%), 30 mg/kg (TGI = 55% to 111%), 60 mg/kg (TGI = 52% to 111%), and 120 mg/kg (TGI = 104% to 111%) in these PDX models. Study 17RAD211 included a follow-up period, which revealed that tumours did not regrow until 3 weeks after last dosing. Nevertheless, this finding suggests that resistance to elacestrant manifests rather quickly. This issue was discussed by the Applicant by referring to the publication of Pancholi et al., 2022 describing the loss of sensitivity to elacestrant in the long-term oestrogen-deprived (LTED) T47D cell line, which results from the loss of ERα. The same

paper reports that culturing MCF7-LTEDY537C cells with 1000 nM elacestrant for a long time leads to elacestrant resistance associated with the upregulation of EGFR and IGF-1R.

The pharmacology of elacestrant is known to be biphasic (tumour growth was observed at 1 and 3 mg/kg by Wardell et al.), with agonist activity at lower doses and antagonist activity at higher doses. The Applicant was asked to clarify whether the expected antagonistic pharmacological effect will be elicited at the concentrations observed in patients. From the applicant's discussion of non-clinical and clinical data it is deemed reassuring that with the proposed dosing recommendations and resultant expectable exposure ranges in the target population an agonistic effect of elacestrant even after crossing the blood-brain barrier can be excluded.

The *in vivo* studies differed with respect to cell type (cell line / patient derived), duration of treatment, route of administration and used dosage of elacestrant, but also fulvestrant, palbociclib and other type of anti-tumour treatments. Therefore, it is difficult to draw conclusions on the efficacy of elacestrant in different type of tumours and also in comparison to fulvestrant, or other type of treatments for these types of breast cancer.

Upon request, the Applicant provided a comparison on the *in vitro* IC50 values of elacestrant and fulvestrant. It appeared that fulvestrant induced a complete degradation at ≥ 10 nM in all cell lines (and this hindered the estimation of IC50 values), whereas at this concentration of elacestrant, a residual band was still present, indicating that fulvestrant was more potent than elacestrant in inducing ER degradation. Indeed, the IC50 of fulvestrant for inducing ERα degradation in MCF-7 cells was estimated to be 0.06 nM (Weir et al., 2016) and fulvestrant was found to be about 10- to 100-fold more effective at ER degradation than elacestrant. The concentration of elacestrant that induces 50% degradation of ER overlaps the range of the antiproliferative effect (50 - 100 nM), and the mean clinical concentration at 354 mg/day, which is 119 ng/ml (equivalent to 261 nM, considering the molecular weight of elacestrant as free base). It can be agreed that elacestrant has potential to inhibit ER, however on the molecular level it is not superior to fulvestrant (~10-fold less potent).

Furthermore, the Applicant was requested to discuss the mechanistic background of different clinical efficacy of elacestrant in patients featuring the wild-type and mutant ESR1 considering similar growth inhibitory effect of in MCF-7 cells with wt- and mt-ESR1 and binding affinity constants. The Applicant referred to a publication of Bihani et al., were IC50 value was measured for different mutant forms of ERα. The publication reported that "the affinity of elacestrant on wild type ERα (IC50 of 42 ± 5.3 nM) was similar to the affinity displayed on a panel of mutant receptors such as ESR1-D538G (56 ± 4.9 nM), ESR1-Y537C (30 ± 5.2 nM), ESR1-Y537N (41 ± 5.7 nM), ESR1-Y537S (61 ± 1.7 nM), and ESR1-S463P (53 ± 2.0 nM), which was confirmed when measuring the transcriptional activity." However, "cotreatment of cells with both elacestrant and E2 resulted in a dose-dependent decrease in E2-induced proliferation, with IC50 values for elacestrant of 27 nM, in the presence of 0.1 nM E2." The Applicant also noted that "the IC50 values of elacestrant for the inhibition of the growth of MCF-7 ESR1-Y537S, or MCF-7 ESR1-D538G cells sensitive to CDK4/6 inhibitors (or those resistant to palbociclib, ribociclib, and abemaciclib) were numerically higher than the value for the growth inhibition of MCF-7 ESR1--WT (15.9, 4.2, and 0.17 nM, respectively, see Patel et al., 2019)". It is thus suggested that although the affinity of elacestrant for ER-wt and ER-mutants is similar, the potency of elacestrant in cells expressing wild type ESR1 depends on the levels of E2, whereas the effect on cells expressing ER-mutants could be relatively independent on E2 levels. However, it is not clear whether ER levels are equal in these different cell lines, whereas this can play a role in the determination of the IC50. Therefore, clinical data is needed to define the activity of elacestrant in different indicated populations (all or not pretreated with CDK4/6 inhibitors or aromatase inhibitors and ER-status) (see clinical aspects).

The Applicant was also asked to discuss the impact of the differences in tumour type model (also comment on the HER-2 status), doses, duration and Route of Administration (RoA) and their effect on the final result with regard to the *in vivo* studies. For plasma exposure values after fulvestrant dosing, the applicant referred to a paper from Bihani et al., that communicated on exposure to subcutaneously (SC) administered fulvestrant to non-tumour bearing mice. The applicant claimed exposure to SC fulvestrant was comparable to fulvestrant exposure after IM administration of Faslodex (as indicated) in the clinic, although the applicant did not comment on whether T ½ values were similar or not. Furthermore, elacestrant exposure data from one of the *in vivo* studies suggest that a dose of 30 mg/kg/day per os (PO) will result in exposure values that can also be reached in the clinic. To conclude, for both SERDs tested, exposure values comparable to clinical exposure values can be reached in the animals.

Elacestrant has been tested for its inhibitory effect on ER related tumour growth *in vitro* and *in vivo* using a lot of different tumour cell lines or patient derived tumour cells that were either or not pretreated with endocrine therapy, aromatase inhibitors, CD4/6 inhibitors or another SERD, fulvestrant. In the *in vivo* experiments, the ER positive tumour cells were subcutaneously injected in different strains of immunocompromised mice. Animals were treated with various doses of elacestrant, all or not in combination with other types of treatment, in studies with different duration. In most of the studies elacestrant alone or combined with other treatments was able to provide inhibition of tumour growth. The *in vivo* data also provided an indication that elacestrant (>30 mg/kg) was able to inhibit the growth of human epidermal growth factor receptor 2 (HER2) positive (e.g., ST986) and of HER2 negative (e.g., HBCx-21) tumour cells.

Thus, these data provide support for the concept of elacestrant as an ER-positive-tumour growth inhibitor *in vitro* or in xenograft animal models. However, the circumstances in a 'petri-dish' or in an immunocompromised mice with tumour cells injected subcutaneously (lacking blood vessel innervation, the tumour microenvironment, the immune cells and all other patient specific factors) are so different from tumours and their activity in the patient that the provided *in vivo* data are only valuable in providing proof of concept. Positive results with elacestrant in *in vitro* tumour type models supported by positive results in *in vivo* animals studies with that certain type of tumour cells may provide rationale for use in a clinical study with the certain type of tumour. However, it cannot provide support for inclusion of certain tumour types in the indication without clear clinical evidence.

In secondary pharmacology studies, it was determined in an *in vitro* assay that elacestrant at 1 µM resulted in inhibition of CNR1 (99% inhibition), ERβ (98% inhibition), growth hormone secretagogue (GHS, ghrelin; 51% inhibition), motilin (71% inhibition), and somatostatin sst1 (52% inhibition) receptors. Although elacestrant binds CNR1 and ADRA2A, in cell-based assays elacestrant did not exhibit CNR1 or CNR2 functional activity either as agonist or as antagonist, nor did elacestrant exhibit agonist or antagonist properties for ADRA2A. At the anticipated peak blood concentration (free fraction of Cmax of 2.09 ng/mL at 500 mg/day, corresponding to 4.6 nM), elacestrant would not be expected to mediate pharmacological responses via ADRA2A. *In vivo*, elacestrant antagonized the uterotrophic effects of E2 in a dose-dependent manner (0.1 to 10 mg/kg). Elacestrant treatment showed a weak oestrogen-like agonist activity by decreasing serum LH in ovariectomized rats and elacestrant mediated protection against bone loss was achieved at least in part by a reduction in bone resorption, as shown by a reduction in urinary deoxypyridinoline at 4 weeks. Furthermore, elacestrant may be effective in modulating vasomotor instability associated with declining ovarian function.

A study in mice with MCF-7 tumours implanted intracranially suggested elacestrant ability to cross the blood-brain barrier. In patients, elacestrant was observed to penetrate the blood-brain barrier in a dose-dependent manner. However, when following the proposed dosing recommendations and resultant expectable exposure ranges in the target population an agonistic effect of elacestrant even after crossing the blood-brain barrier is not expected.

A comparison of *in vitro* hERG inhibition (IC50 187 ng/mL) and estimated unbound elacestrant concentration of 2.7 ng/mL in monkey plasma at 50 mg/kg (a dose that was shown to be devoid of any QT interval effects) showed an approximately 69-fold safety margin for QT related effects via hERG inhibition. It should be noted however, that the PR interval decreased (6% to 11% relative to time-matched controls) on Day 7 for a 500 mg dose QD in patients. At that time, the maximum estimated unbound concentration of elacestrant in human plasma was approximately 2.09 ng/mL (assuming approximately 99% protein binding). This was observed at doses ≥ 50 mg/kg, which may indicate for a low risk for adverse cardiovascular effects at the human therapeutic dose level). At the same time, it should be noted that ECG measurements in repeated dose toxicity studies (4 weeks up to 50 mg/kg or for 39 weeks up to 30 mg/kg) did not show cardiac effects, which is reassuring for the absence of cardiac safety effects of the product. No CNS or respiratory effects were noted in rats treated with a single dose of elacestrant up to 100 mg/kg and no substantial bleeding risk or change in wound healing was observed following elacestrant treatment up to 50 mg/kg for 7 days in rat. Elacestrant treatment (30 and 100 mg/kg/day by oral gavage for 7 days) resulted in emetic events (retching and vomiting) in ferrets, which occurred more frequently at higher doses. However, the number of emesis observations decreased over the duration of the study, suggesting that elacestrant was becoming more tolerable in the animals following repeated dosing.

The absence of dedicated pharmacodynamics interaction studies can be agreed. Combination of elacestrant with palbociclib and everolimus in primary pharmacology studies showed additive potential with regard to anti-tumour effect.

Pharmacokinetics

Overall, the pharmacokinetics of elacestrant have been well studied in the rat, but only partially in monkeys even though this is a pivotal animal species.

General pharmacokinetic parameters seemed to be comparable between non-clinical species and humans. Sex differences were observed for rats, but not in monkeys and humans. Bioavailability and excretion were comparable between pre-clinical species and humans, however, differences were noted between the *in vivo* metabolism between rats and humans.

In vivo studies for distribution, metabolism and excretion were only performed in rats. Although all pharmacokinetic aspects are covered by the rat studies, an explanation for the lack of studies in monkeys regarding blood:plasma distribution and metabolism was asked from the applicant. The Applicant acknowledged the lack of a blood:plasma partitioning study in monkeys, but argued that no haematotoxicity was observed in the single- and repeat dose toxicity studies in monkeys and there were no effects on coagulation. Therefore, investigation of potential accumulation in blood cells in monkeys was not deemed necessary.

Regarding the missing *in vivo* metabolism study in monkeys, the Applicant notes that coverage of human major metabolites was not deemed necessary according to ICH guideline S9. Furthermore, a good clinical safety profile was established for elacestrant. Therefore, it is not expected that human major metabolites have a significant impact on human safety at the selected dose, regardless of their exposure in monkeys.

It appears that the bioavailability increased with increase in dose resulting in a more than dose proportional increase in Cmax and AUC. However, at much higher doses (100-900 mg/kg) the increase was less than dose proportional, indicating a limit to the increase in bioavailability or potentially even a decrease. In humans, the bioavailability was assessed at one dose (below therapeutic dose) and was 10%, however, at higher doses the bioavailability in humans may be higher and should be considered in the assessment of clinical findings.

Furthermore, elacestrant was highly bound to the proteins in rat, monkey, and human plasma (approximately 99% binding). The percent unbound values were similar across the species, being 1.61%, 0.918% and 1.00% in rat, monkey and human plasma respectively, and did not show the concentration dependence over the tested concentration range. However, when interpreting toxicological and clinical safety data the exposure based on free fraction should be used and not the total exposure. Exposure margins were re-calculated based on free fraction AUCs, since the applicant calculated them using the total AUCs. The exposure margins were small but sufficient.

Lastly, metabolite M1 was a major metabolite *in vivo* in male rats (28.1%) but not in female rats (8.85%). In clinical human studies, the major metabolite in plasma was M16 (41.3%, a glucoronidation of M1) and parent elacestrant was only 5.2%. In rat plasma, M16 (a glucuronide of M1) accounted for 7.3% in males and 5.4% in females. Due to missing data the metabolic profile in monkeys is not known. As the metabolite M16 was adequately qualified in the rat toxicological studies, no issues for clinical safety are foreseen. The excretion in humans appeared to be similar to the excretion in rats, with the faeces as the predominant route of elimination, low recovery in urine, presence of circulating metabolites and only very low clearance of parent elacestrant in urine.

Studies in human liver microsomes and with recombinant enzymes revealed that elacestrant was a substrate of CYP3A4 with a minor contribution of CYP2A6 and CYP2C9. Of note, no reaction phenotyping studies for UGTs were submitted, which is acceptable given that glucuronidation reactions represent only secondary metabolism.

A risk of clinically relevant intestinal CYP3A4 inhibition above the threshold exists for elacestrant at the dose of 400 mg (345 mg free base) if a basic model is used for the estimation. Data from an evaluation of enzyme induction (CYP1A2, CYP2B6 and CYP3A4) in cryopreserved human hepatocytes in a collagen-sandwich configuration on the mRNA level were presented. Cytotoxicity was shown by LDH release at concentrations above 10 µM. Therefore, only concentrations up to 3 µM were analysed for mRNA induction. Respecting the nominal free concentration after correction for protein binding in incubation medium, the three analysed doses (0.3, 1 and 3 µM) were in the recommended range for analysis as 3 µM were above a 50-fold $C_{max,u}$ at the maximum recommended daily dose of 345 mg elacestrant. Enzyme induction was in general low for all 3 enzymes and below 100% induction (2-fold) except for CYP1A2 in one donor. EC_{50} and E_{max} was not determined due to the high variability. Irrespective if the increase in CYP1A2 mRNA induction was concentration dependent for the analysed range of 0.3 up to 3 µM, the observed increase represented only 3% of the prototype inducer omeprazole and was therefore below the cut off (20% of model inducer) for an inducer according to CPMP/EWP/560/95/Rev. 1 Corr. 2**. CYP2C enzymes were not further analysed due to negative results for CYP3A4 mRNA induction and the fact that both enzymes share the same signalling pathway (PXR) for induction. The Applicant argues that Ki can be estimated based on half-maximal inhibitory concentration (IC_{50}) as per draft ICH Guidance M12 on drug interaction studies (EMA/CHMP/ICH/652460/2022). The Applicant's estimation of Ki as $IC_{50}/2$ according to Haupt et al., 2015 is agreed. The Applicant's position that the systemic DDI risk for CYP3A4 inhibition by elacestrant is low is also agreed. In addition, elacestrant is not expected to inhibit intestinal CYP3A4 activity at clinically relevant concentrations up to the exposure obtained at the therapeutic dose of 400 mg QD of elacestrant dihydrochloride (345 mg elacestrant). Hence, no *in vivo* study of the CYP3A4 inhibitory potential of elacestrant is required, regardless of the results of the basic model estimations or the static mechanistic model (CPMP/EWP/560/95/Rev. 1 Corr. 2**).

The involvement of BCRP in the transport of elacestrant was evaluated in a BCRP overexpressing MDCKII-BCRP monolayer assay for bidirectional permeability. Elacestrant was evaluated at 0.3, 3, 30 and 300 µM in a vesicular transport substrate assay using inside-out membrane vesicles from cells overexpressing human ABCG2 (BCRP) transporter. No significant transport or accumulation was determined for elacestrant after initiation of the reaction by either ATP or AMP. In addition, the

combination with a BCRP inhibitor did not change the ATP/AMP-dependent accumulation. Non-specific binding of elacestrant to the surfaces of plastic ware was evaluated in the presence of control vesicles. Elacestrant showed non-specific binding at concentrations above 3 µM, which resulted in a lower accuracy than the nominal concentration (~70%), which was further reduced by 30-50% by the end of the incubation time. This effect limits the value of the data. In conclusion, although the data of both assays confirmed that elacestrant is not transported by BCRP, the value of these data is limited due to cytotoxicity at relevant higher concentrations in the monolayer assay and high non-specific binding in the vesicular transport substrate assay. Nevertheless, taking into account that elacestrant had been shown to be a low permeability substance in Caco-2 cells (see below) no overall clinical impact on DDI due to BCRP transport is expected.

The Applicant investigated bidirectional permeability of elacestrant in Caco-2 cells. Overall, elacestrant was found to be a low permeability compound. Based on these findings, the Applicant concluded that elacestrant is not a substrate of MDR1 (P-gp). This conclusion should, however, be supported by studies with MDR1-transfected cells and competition studies with P-gp substrates. The Applicant will conduct a study in MDR1-overexpressing cells with and without P-gp inhibitors to clarify whether elacestrant is a P-gp substrate (REC). The results will be available by the end of December 2023 (Results submission: January 2024). As the bidirectional permeability study in Caco-2 cell earlier showed low permeability of elacestrant in both directions, the probability of clinically relevant P-gp-mediated interference with the PK of elacestrant is considered relatively low. Therefore, conducting the above-mentioned study in MDR1-overexpressing cells post-approval is acceptable.

Toxicology

The Applicant provided a justification for the use of non-human primates as non-rodent species, indicating that morphological and hormonal changes in the reproductive system and menstrual cycle phases of monkeys closely resemble those of humans.

Several single-dose oral toxicity studies with elacestrant have been conducted in female Sprague Dawley (SD) rats at doses up to 1200 mg/kg and in female Cynomolgus monkeys at doses up to 500 mg/kg. Repeat-dose oral toxicity studies with elacestrant have been conducted in SD rats at doses up to 900 mg/kg for up to 26 weeks, and in Cynomolgus monkeys at doses up to 1000 mg/kg for up to 39 weeks. Initial studies were only performed in female animals, but later studies were conducted in both sexes.

In general, treatment with elacestrant displayed a similar toxicity profile *in vivo* as compared to fulvestrant. Female rats and monkeys displayed decreased weight and atrophy of the uterus, vagina, cervix, and mammary gland, increased weight of the ovaries correlating with the presence of follicular cysts, and atrophy of the pituitary gland (only in rats). Male rats displayed decreased body weight (gain) and reduced food intake. These findings are likely caused by the antagonistic effect of elacestrant on the tropic effects of 17β-oestradiol (E2) and hormone feedback mechanisms.

In contrast, male monkeys had increased weights of the pituitary gland. The Applicant provided a discussion on the mechanism behind the increase in basophilic pituicytes in the pituitary gland and subsequent increased weight of the pituitary gland in male monkeys. However, the mechanism behind the increase in basophilic pituicytes in the pituitary gland and subsequent increased weight of the pituitary gland in male monkeys remains unclear. Since this isolated finding was reversible upon drug discontinuation, and taking into account the indication, it does not represent a major safety concern.

In a definitive GLP-compliant single-dose toxicity study in female rats, although there was no clear dose response, increased ALT levels, and increased neutrophil and monocyte counts can be indicative of a transient inflammatory response and possible persistent hepatic injury. Evidence of potential hepatotoxicity was noted in both species. However, the increased liver enzymes, sometimes

accompanied by histopathological findings (vacuolated hepatic biliary epithelial cells) in the liver, did not show a consistent correlation in either monkeys or rats, and showed inconsistent changes between sexes. In addition, vasculitis and/or perivasculitis was only observed at a nearly lethal dose in monkeys, and therefore the clinical relevance is likely low.

Hypoalbuminemia was observed in rats. However, no hypoalbuminemia was observed in monkeys and no drug-related hypoalbuminemia was observed in clinical trials with elacestrant. Therefore, this finding is not considered relevant for humans. It can be concluded that the findings in non-clinical studies did not identify hepatoxicity as an important risk.

Finally, general toxicity studies additionally revealed treatment-related findings in the stomach and small intestine in both rats and monkeys which are considered relevant for humans.

In conclusion, elacestrant displayed low acute toxicity. In repeated dose toxicity studies in rats and monkeys, the antiestrogenic activity of elacestrant was responsible for the effects seen, particularly in the female reproductive system, but also in other organs sensitive to hormones such as mammary gland, pituitary and testes. Sporadic emesis and diarrhoea were recorded in monkeys. In addition, in long-term studies (26 weeks in rats and 39 weeks in cynomolgus monkeys), increased vacuolation of the mucosal epithelium of the non-glandular stomach were observed in rats and vacuolated macrophage infiltrates in the small intestine were recorded in both rats and monkeys. In monkeys this effect occurred at a level of systemic exposure of about 70% of the human exposure. (See SmPC section 5.3).

Elacestrant showed no genotoxic potential in the Ames test, chromosomal aberrations in human lymphocytes and in the micronucleus assay in rats (See SmPC section 5.3).

No carcinogenicity studies with elacestrant were submitted which is in line with ICH S9 Guidance for Nonclinical Evaluation for Anticancer Pharmaceuticals (2009) and deemed acceptable.

No fertility or early embryonic development studies with elacestrant were submitted, which is deemed acceptable. In repeated-dose toxicity studies effects related to fertility were observed in rat and monkey female reproductive tract these effects occurred below human exposures at MRHD (maximum recommended dose). Decreased cellularity of Leydig cells in rat testes was also observed at exposure levels 2.7-fold higher than in humans (see SmPC section 5.3).

Based on the well-known mechanism of action of SERDs, adverse effects on male and female fertility can be anticipated (See SmPC section 4.6). In embryo-foetal development studies in rats, oral administration of elacestrant resulted in maternal toxicity (body weight loss, low food consumption, red vulvar discharge) and increased resorptions, increased post-implantation loss, and reduced number of live foetuses and foetal variations and malformations below human exposures at MHRD. In line with the mechanism of action of elacestrant, the observed findings in dams and foetuses were expected. Women of childbearing potential should be advised to use effective contraception during treatment with Orserdu and for one week after the last dose (See SmPC section 4.6). There are no data from the use of elacestrant in pregnant women. The pregnancy status of females of reproductive potential should be verified prior to starting treatment with Orserdu. If pregnancy occurs while taking Orserdu, the patient must be informed of the potential hazard to the foetus and potential risk of miscarriage (see SmPC section 4.6). It is unknown whether elacestrant/metabolites are excreted in human milk. Because of the potential for serious adverse reactions in the breast-fed infant, it is recommended that lactating women should not breast-feed during treatment with Orserdu and one week after the last dose of (see SmPc section 4.6). Based on findings from animal studies (see section 2.5.4.5.) and its mechanism of action, elacestrant may impair fertility in females and males of reproductive potential (see SmPC sections 4.6 and 5.3).

No pre- and postnatal development study or study in juvenile animals was submitted. In line with the proposed indication, as per ICH guideline S9 on nonclinical evaluation for anticancer pharmaceuticals this is considered acceptable.

A GLP-compliant local tolerance study was conducted in male New Zealand white rabbits, with IV and perivenous administration of elacestrant. No treatment-related findings occurred, and elacestrant was locally well tolerated. Since elacestrant is intended for oral administration, this study is of limited relevance.

No dedicated studies on antigenicity, immunotoxicity or dependence were performed. No studies with elacestrant metabolites were performed. This is acceptable. The impurities present in the drug substance or intermediates to the drug product were adequately evaluated based on *in silico* predictions. Additionally, impurities exceeding the qualification limits were adequately qualified in repeat-dose toxicity studies.

A GLP-compliant neural red uptake phototoxicity assay in BALB/c 3T3 mouse fibroblasts was conducted with elacestrant. The photo irritation factor was ≤ 1.118 and the mean photo effect was ≤ 0.001, indicating no phototoxic potential of elacestrant.

Elacestrant dihydrochloride is potentially PBT/vPvB, the PBT assessment cannot be finalised in absence of the required studies. For Tier A only a ready biodegradability test is provided that is considered unreliable. The substance was toxic to the inoculum, and the test should be repeated as per OECD TG 301 (section 25). The applicant should consider performing the activated sludge, respiration inhibition test (OECD TG 209) prior to repeating the OECD TG 301 test as this test could provide information on the toxicity and the appropriate test concentration.

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of elacestrant to the environment. The applicant commits to perform the following studies and provide the expert reports and study reports by end of 2026:

- Bioaccumulation in fish (OECD TG 305);
- Adsorption-desorption using a batch equilibrium method (OECD 106) using 3 soil types and 2 types of sewage sludge;
- Ready biodegradability test (OECD 301);
- Aerobic and anaerobic transformation in aquatic sediment systems (OECD 308);
- Algal growth inhibition test (OECD 201);
- Daphnia sp. reproduction test (OECD 211, use version 2012);
- Fish, Full Life Cycle Test (OECD 240);
- Activated sludge, respiration inhibition test (OECD 209, use version 2010)

For all studies the original study report must be submitted. From all requested chronic toxicity studies and the OECD 209 test, a NOEC and/or EC10 is needed for the risk assessment. In case a limit test is performed, the OECD guidelines should be followed: if the limit test results in a statistically significant effect, a new test to determine a dose-response relationship should be performed, from which a NOEC and/or EC10 should be reported.

If the outcome of the adsorption study (OECD 106) is that Koc >10,000 L/kg, a risk assessment for the terrestrial compartment is triggered, unless the compound is found readily biodegradable (OECD 301). In case a terrestrial risk assessment is triggered, the following tests are required:

- Aerobic and anaerobic transformation in soil (OECD 307),
- Soil Micro organisms: Nitrogen Transformation Test (OECD 216),
- Terrestrial plants, growth test (OECD 208, use version 2006),
- Earthworm, acute toxicity tests (OECD 207),

- Collembola, reproduction test (OECD 232).

If significant shifting to the sediment is observed (more than 10% at any time-point at or after 14 days is present in the sediment) in the OECD 308 water:sediment simulation study (unless the compound is found readily biodegradable), effects on a sediment dwelling organism should be investigated and compared to the PECsediment. Applicable tests are those with:

- Hyalella sp; Lumbriculus sp. (OECD 225) or
- Chironomus sp. (OECD 218 or 219).

2.5.7. Conclusion on the non-clinical aspects

The non-clinical data package evaluating the pharmacology and toxicity of elacestrant is considered acceptable to support the marketing authorisation taking into account the applicant's commitment to conduct a study in MDR1-overexpressing cells with and without P-gp inhibitors to clarify whether elacestrant is a P-gp substrate (REC) and ERA commitments (REC).

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 18: Overview of the clinical studies relevant to elacestrant clinical pharmacology

Study type	Study Number/ Study Phase	Study Objective(s)	Key Design	Study Population Number of Subjects (M/ F) Median Age (Min, Max)	Treatment
Phase 1 Study					
healthy subject pharmacokinetics studies	RAD-1901-001/ Phase 1	Safety, tolerability, and single- and multiple-dose PK of elacestrant; bioavailability; ascending dose; and food effect	Single-ascending and Multiple ascending-dose PK	Postmenopausal women Healthy subjects N=80 SAD n=32 (24 elacestrant/8 placebo) (0 male/32 female) 66 (57, 75) years MAD: n=48 (38 elacestrant/10 placebo) (male 0/female 48) 62 (50, 75) years	SAD: Elacestrant or placebo Group 1: 1 and 25 mg capsule, fasted Group 2: 10 and 200 mg capsule, fasted Group 3: 50 mg capsule, fasted and fed Group 4: 100 mg capsule and 1 mg IV, fasted MAD: Elacestrant 10, 25, 50, 100, and 200 mg capsule or placebo QD for 7 days

Study type	Study Number/ Study Phase	Study Objective(s)	Key Design	Study Population Number of Subjects (M/ F) Median Age (Min, Max)	Treatment
healthy subject pharmacokinetics studies	RAD1901-004/ Phase 1	MTD, safety, tolerability, PD, and PK of elacestrant and elacestrant concentrations in CSF	Multiple-dose PK	Postmenopausal women Healthy subjects N=52 (44 elacestrant/8 placebo) (0 male/52 female) Mean age: 59 to 64 (50, 75) years across groups	Elacestrant 200, 500, 750, and 1000 mg capsule or placebo QD for 7 days
Extrinsic factor studies	RAD1901-109/ Phase 1	Effect of food on elacestrant PK	Single-dose food effect	Postmenopausal women and men Healthy subjects N=18 (9 male/9 female) 58 (42, 73) years	Elacestrant 400 mg tablet, single oral dose on Day 1 of each period
Extrinsic factor studies	RAD1901-110/ Phase 1	Effect of strong CYP3A4 inhibitor itraconazole on elacestrant PK	DDI	Postmenopausal women and men Healthy subjects N=18 (9 male/9 female) 59 (40, 70) years	Elacestrant 200 mg tablet QD for the first 7 days followed by elacestrant 200 mg tablet QD coadministered with itraconazole 200 mg capsule QD for the next 7 days

Study type	Study Number/ Study Phase	Study Objective(s)	Key Design	Study Population Number of Subjects (M/ F) Median Age (Min, Max)	Treatment
healthy subject pharmacokinetics studies	RAD1901-111/ Phase 1	Absorption, metabolism, distribution, and excretion of ^{14}C-elacestrant	ADME (mass balance)	Men Healthy subjects N=7 (7 male/0 female) 40 (26, 55) years	^{14}C-elacestrant 400 mg capsule, single oral dose

Study type	Study Number/ Study Phase	Study Objective(s)	Key Design	Study Population Number of Subjects (M/ F) Median Age (Min, Max)	Treatment
	RAD1901-112/ Phase 1	Relative bioavailability (2 prototype tablets compared to clinical tablet) and food effect	Relative bioavailability and food effect	Postmenopausal women and men Healthy subjects N=36 (27 male/9 female) Cohort 1: N=18 (14 male/4 female) 49 (40, 58) years Cohort 2: N=18 (13 male/5 female) 53 (42, 59) years	Cohort 1: Single, oral doses of each of the following: Treatment A: elacestrant 400 mg, fed Treatment B: Prototype 1 400 mg, fasted Treatment C: Prototype 1 400 mg, fed Cohort 2: Single, oral doses of each of the following: Treatment A: elacestrant 400 mg, fed Treatment D: Prototype 2 400 mg, fasted Treatment E: Prototype 2 400 mg, fed

Study type	Study Number/ Study Phase	Study Objective(s)	Key Design	Study Population Number of Subjects (M/ F) Median Age (Min, Max)	Treatment
Extrinsic factor studies	RAD1901-113/ Phase 1	Effect of strong CYP3A4 inducer rifampin on elacestrant PK	DDI	Postmenopausal women and men Healthy subjects N=18 (12 male/6 female) 56 (43, 74) years	Treatment A: elacestrant 400 mg tablet, single oral dose on Day 1, Period 1 Treatment B: rifampin 600 mg QD (2×300 mg capsules) on Days 1 to 14; with single oral dose of elacestrant 400 mg tablet on Day 7, Period 2, approximately 1.5 hours after rifampin dose
Extrinsic factor studies	RAD1901-114/ Phase 1	Effect of highly protein-bound drugs warfarin and elacestrant on each other's PK	DDI	Postmenopausal women and men Healthy subjects N=18 (12 male/6 female) 54 (42, 60) years	Treatment A: elacestrant 400 mg tablet, single oral dose on Day 1 Treatment B: warfarin 25 mg (2×10 mg and 1×5 mg tablets), single oral dose on Day 1 Treatment C: elacestrant 400 mg tablet coadministered with warfarin 25 mg (2×10 mg and 1×5 mg tablets), single oral dose on Day 1

Study type	Study Number/ Study Phase	Study Objective(s)	Key Design	Study Population Number of Subjects (M/ F) Median Age (Min, Max)	Treatment
Extrinsic factor studies	RAD1901-115/ Phase 1	Effect of proton pump inhibitor omeprazole on elacestrant PK	DDI	Postmenopausal women and men Healthy subjects N=18 (13 male/5 female) 50 (40, 59) years	Treatment A: elacestrant 400 mg tablet, single oral dose on Day 1, Period 1 Treatment B1: multiple QD doses of omeprazole 40 mg capsules on Days 1 to 5 prior to elacestrant 400 mg tablet coadministration on Day 5, Period 2 Treatment B2: multiple QD doses of omeprazole 40 mg capsules on Days 5 to 12 following elacestrant tablet coadministration on Day 5, Period 2

Study type	Study Number/ Study Phase	Study Objective(s)	Key Design	Study Population Number of Subjects (M/ F) Median Age (Min, Max)	Treatment
Special population	RAD1901-117/ Phase 1	Effect of mild or moderate hepatic impairment on elacestrant PK	Non-randomized, open-label, parallel-group, hepatic impairment	Women and men with mild and moderate hepatic impairment or healthy subjects N=36 Normal hepatic function: N=16 (11 male/5 female) 58 (51, 68) years Mild hepatic impairment: N=10 (5 male/5 female) 64 (49, 75) years Moderate hepatic impairment: N=10 (9 male/1 female) 60 (48, 71) years	Elacestrant 200 mg (2×100 mg tablets), single oral dose

Study type	Study Number/ Study Phase	Study Objective(s)	Key Design	Study Population Number of Subjects (M/ F) Median Age (Min, Max)	Treatment
Extrinsic factor studies	RAD1901-118/ Phase 1	Effect of elacestrant on the digoxin and rosuvastatin PK in healthy subjects (transporter mediated DDI: P-gp and BCRP)	DDI	Women and men Healthy subjects Cohort 1: Digoxin: N=15 (12 male/3 female) 53 (26, 59) years Cohort 2: Rosuvastatin: N=21 (14 male/7 female) 56 (22, 72) years	Cohort 1: Single, oral doses of the following: Day 1: digoxin 0.5 mg (2×0.25 mg tablets) Day 9: digoxin 0.5 mg (2×0.25 mg tablets) + elacestrant 400 mg tablet Cohort 2: Single, oral doses of the following: Day 1: rosuvastatin 20 mg tablet Day 6: rosuvastatin 20 mg tablet + elacestrant 400 mg tablet

Table 19: Overview of the clinical studies evaluating elacestrant in subjects with advanced/metastatic breast cancer

Study ID Number of Sites/Countries Study Start/ Status	Study Design	Treatments Administered	Efficacy Objectives	Number of Subjects (Actual)	Study Population	Efficacy Endpoints
Phase 3 Study (Pivotal)						
RAD1901-308 (Study 308) 150 sites in 17 countries May 2019 to Sep 2021 (DCO) Complete for PFS; ongoing for OS	Open-label, multisite, randomized, active-controlled, event-driven study	Elacestrant 400 mg QD PO SOC: Fulvestrant 500 mg IM[a] Anastrozole 1 mg QD PO Letrozole 2.5 mg QD PO Exemestane 25 mg QD PO	Primary: To demonstrate that elacestrant, when compared with the SOC options of either fulvestrant or an AI, is superior in prolonging PFS based on a blinded IRC assessment in postmenopausal women and men with ER+/HER2- mBC either in *ESR1*-mut subjects or in all subjects (*ESR1*-mut + *ESR1*-mut-nd) Key Secondary: To compare OS between treatment groups in *ESR1*-mut subjects and in all subjects (*ESR1*-mut + *ESR1*-mut-nd)	478 subjects (228 *ESR1*-mut and 250 *ESR1*-mut-nd) 1:1 randomization to either elacestrant or SOC	Postmenopausal women and men with ER+/HER2- mBC whose disease had relapsed or progressed on 1 or 2 prior lines of endocrine therapy for mBC, which must have included prior CDK4/6 inhibitor therapy in combination with fulvestrant or an AI, including those with tumours that have been determined to be *ESR1*-mut positive	Primary: IRC-assessed PFS in *ESR1*-mut subjects IRC-assessed PFS in all subjects (*ESR1*-mut + *ESR1*-mut-nd)

Table 19 Overview of the clinical studies evaluating elacestrant in subjects with advanced/metastatic breast cancer (Continued)

Study ID Number of Sites/Countries Study Start/ Status	Study Design	Treatments Administered	Efficacy Objectives	Number of Subjects (Actual)	Study Population	Efficacy Endpoints
Phase 1 Studies						
RAD1901-005 (Study 005) 11 sites in the US Apr 2015 to Oct 2019 Completed	Open-label, multisite, multipart, dose-escalation study Part A: dose escalation Part B: safety expansion Part C: safety expansion Part D: dose exploration	Elacestrant 200, 400, and 600 mg QD; capsules and tablets	To determine the MTD and/or RP2D of elacestrant in subjects with ER+/HER2- mBC and to evaluate the preliminary anti-tumour effects of elacestrant	57 subjects Part A: 13 Part B: 20 Part C: 14 Part D: 10	Postmenopausal women with advanced ER+/HER2- breast cancer	Tumour response as assessed by the investigator using RECIST v1.1
RAD1901-106 (Study 106) 5 sites in Europe Feb 2016 to Aug 2018 Completed	Open-label, nonrandomized, multisite, 2 dose cohort study	Elacestrant 200 and 400 mg QD; capsules and tablets	To determine the effect of elacestrant on ER expression and oestradiol (E2) binding to the ER in metastatic breast cancer lesions as measured by FES-PET imaging and to evaluate the preliminary anti-tumour effects of elacestrant	16 subjects	Postmenopausal women with histologically-confirmed, ER+/HER2- metastatic breast cancer	Tumour response as assessed by the investigator using RECIST v1.1

Abbreviations: AI = aromatase inhibitor; CDK4/6 = cyclin-dependent kinase 4/6; DCO = data cutoff; ER = oestrogen receptor; ER+ = oestrogen receptor positive; *ESR1* = oestrogen receptor 1 gene; *ESR1*-mut = *ESR1* mutation positive; *ESR1*-mut-nd = no *ESR1* mutation detected; FES-PET = fluoroestradiol-positron emission tomography; HER2- = human epidermal growth factor receptor 2 negative; ID = identifier; IM = intramuscular(ly); IRC = Imaging Review Committee; mBC = metastatic breast cancer; MTD = maximum tolerated dose; OS = overall survival; PFS = progression-free survival; PO = orally; QD = once daily; RECIST v1.1 = Response Evaluation Criteria in Solid Tumours version 1.1; RP2D = recommended Phase 2 dose; SOC = standard of care; US = United States.

[a] Fulvestrant was administered monthly after 3 biweekly doses.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Absorption

In vitro, elacestrant showed low permeability across Caco-2 cells and was not a substrate of P-gp. Under fasted conditions, oral absorption of elacestrant was rapid (tmax ~ 4 hours) and the absolute bioavailability was approximately 10%.

Following oral administration, elacestrant was rapidly absorbed, reaching Cmax within 1-4 hours. The geometric mean Cmax was 52.86 ng/mL (35.2% CV) and AUCinf was 1566 ng*h/mL (38.4% CV) after single dose administration of 345 mg of elacestrant in fed conditions. At steady state, the median [min, max] plasma concentration at 4h post-dose (C4h) and AUC are predicted to be 108 ng/mL [27.5 – 351] and 2190 ng*h/mL [461 -8470], respectively (See SmPC section 5.2).

Concentration-curves in single and multiple dose showed a second peak around 4-6 hours and also further peaks/shoulders at very late (>50 hours) time points. Enterohepatic recycling was ruled out because double peaks should be observed regardless of the route of administration. Specifically, for elacestrant, the secondary peaks were observed only after oral administration and not after intravenous administration. Later peaks most likely could result from an acidified microenvironment in the lower GIT that enhances late drug release and absorption.

Elacestrant 100 and 400-mg commercial tablets and elacestrant 100 and 400-mg clinical tablets were shown to be bioequivalent.

Administration of elacestrant 345 mg tablet with a high-fat high-calorie meal increased Cmax and AUC by 40% and 20%, respectively, as compared to fasted administration. When the tablet was co-administered with a light meal, Cmax and AUC increased in a similar fashion, i.e., by 30 and 20%, respectively. Ingestion with food may reduce gastrointestinal side effects (See SmPC section 5.2).

Distribution

Elacestrant was highly bound to the proteins in human plasma (approximately 99%) and did not show the concentration dependence over the tested concentration range.

Volume of distribution

Elacestrant had a very large apparent volume of distribution of 11000-55000 L that appeared to be dose-dependent both at single and repeat dose, with a trend of decreasing Vz/F with increasing dose. After IV administration Vz was 1730 L. Based on population pharmacokinetic analysis, elacestrant is extensively distributed in the tissues with an apparent peripheral volume of distribution of 5411 L. The apparent central volume of distribution of elacestrant at steady state is 422 L (See SmPC section 5.2).

B:P ratio

Total blood and plasma drug-related radioactivity concentration ratios ranged from 0.607 to 0.794, indicating little to no association of radioactivity with blood cellular components.

Penetration of blood brain barrier

Elacestrant was shown to penetrate the blood-brain barrier in a dose-dependent manner. After oral administration of elacestrant 200 mg QD or 500 mg QD for 7 consecutive days, median elacestrant total (bound and unbound) concentration in cerebrospinal fluid was 0.0966 ng/mL for the 200-mg dose group and 0.155 ng/mL for the 500-mg dose group.

Variability

Variability was moderate. There seems to be lower variability in women. High-fat seems to reduce variability more than low-fat meal, and mainly for Cmax.

Elimination

Faecal excretion was the predominant route of elimination for elacestrant (81.5%), with intact elacestrant representing 34%. Elimination with urine was minimal (7.53%). Based on the revised PBPK report, the fraction of drug absorbed from the gut (Fa) was estimated with 42.9%, the fraction of drug escaping first-pass metabolism in the gut (Fg) was 33 % and the fraction of drug escaping first-pass metabolism in the liver (Fh) was 37%.

The arithmetic mean elacestrant t1/2 was approximately 30 hours after single oral administration and increased under multiple dosing up to ~47 hours, independently of dose. The t1/2 of elacestrant after single IV administration was 33.4 hours. In the mass-balance study plasma total radioactivity was ~32-fold higher than plasma elacestrant AUC, for Cmax ~15-fold. The much longer t1/2 of the plasma radioactivity of 165 vs. 35 hours for plasma elacestrant concentration corroborated the large amount of circulating metabolites with slower elimination rate.

Elacestrant renal clearance is very low (≤ 2.3 mL/min) and it was eliminated by oxidative metabolism and faecal excretion.

In the final PopPK analysis, CL/F was 186 L/hour. Apparent clearance increased with increasing dose and was higher after multiple dose. It decreased in fed state compared to fasted.

Dose proportionality and time dependencies

After single dose and at steady-state, Cmax and AUC increased in more than proportional manner. An approximate 2-fold accumulation was observed (for both Cmax and AUC) after 7 days of QD oral administration (Study RAD1901-001) in the dose range of 10 and 200 mg qd. After repeated oral administration, elacestrant CL/F and VZ/F appeared to be higher than after a single dose. The t1/2 also tended to be longer after repeated dosing (31 to 47 hours compared to approximately 30 hours). The tmax was similar after a single dose and at steady-state conditions (< 4 hours).

Pharmacokinetics in the target population

Table 20: Summary of the exposure metrics from Study RAD1901-308 for the E-R Analyses

Summary of the Exposure Metrics from Study RAD1901-308 for the E-R Analyses

Exposure Metric	Statistic	Estimate
AUCss (µg*hr/mL)	Mean (SD)	2.44 (1.08)
	Median (Min-Max)	2.19 (0.461-8.47)
AUCav (µg*hr/mL)	Mean (SD)	2.32 (1.05)
	Median (Min-Max)	2.06 (0.429-8.07)
AUCav PFS (µg*hr/mL)	Mean (SD)	2.25 (1.14)
	Median (Min-Max)	2.03 (0.00-8.07)
Conc4h (ng/mL)	Mean (SD)	119 (51.9)
	Median (Min-Max)	108 (27.5-351)

AUCss: nominal steady-state daily AUC (Dose/CL/F) ; AUCav: average daily AUC derived from cumulative AUC until the last dose; AUCav PFS: average daily AUC derived from cumulative AUC until PFS
Source: RAD1901-308_ERdataset_43v2t.csv; Covariatesummary_ER_43v2t_v1.R; cov_summ_ER_43v2t_v1.csv

From only few PK samples in study 106 in mBC patients that were correlated with positive PD response at D14 from the 200 mg dose a minimal target plasma concentration of 20 ng/ml was derived. This value served as reference in the ER modelling. Simulation of exposure data for mutant vs. wt-ESR1 patients in study 308 receiving 400 mg elacestrant showed comparable Cmax,ss, Cmin,ss and AUCss.

Special populations

No dedicated studies assessing relationship between race and PK of elacestrant exposure were submitted. Race was not formally assessed as a covariate in the population pharmacokinetics due to limited number of subjects other than Caucasian included in the clinical development. However, based on an exploratory analysis, which included PK data from Phase 1 and Phase 3 studies used for the popPK model development, i.e. 79% were Caucasian (N = 353), 5% were Black (N = 22), 4% were Asian (N = 17), 11% missing (N = 47), and 1% other (N = 8), no significant differences in exposure was observed among the different races.

Boxplots of estimated exposure for different age/weight groups were within the observed range of exposures in Study 308 confirming that the extreme group of the eldest subjects (age > 89 years old, i.e., maximum age in popPK dataset) and with very low body weight (< 41.3 kg, i.e., minimum body weight in popPK dataset) did not have increased exposures to a clinically significant level.

A dedicated study in subjects with hepatic impairment was submitted. After administration of 200 mg elacestrant, AUC increased with increasing severity of hepatic impairment. Elacestrant Cmax, AUC0–t, and AUC0–∞ geometric least squares mean ratios for the mild hepatic impairment group were higher. i.e. 11% (90% CI:0.95-1.28), 26% (90% CI:0.84-1.88), and 28% (90% CI:0.85-1.94), respectively, than those for the normal hepatic function group.

Elacestrant Cmax, AUC0–t, and AUC0–∞ geometric least squares mean ratios for the moderate hepatic impairment group were higher, i.e. 14% (90% CI:0.89-1.45), 76% (90% CI:1.30-2.40), and 83% (90% CI:1.32-2.52), respectively, than those for the normal hepatic function group.

The geometric mean t1/2 tended to increase with increasing severity of hepatic impairment, from 39.5 hours in the normal hepatic function group to 46.4 and 54.3 hours in the mild and moderate hepatic impairment groups, respectively.

To evaluate an impact of different degrees of hepatic impairment on PK of elacestrant, the applicant developed a PBPK model. The model predicted a 3.02-fold increase in AUC0-inf and a 1.88-fold

increase in Cmax in subjects with severe hepatic impairment compared to the control group, after a single 400 mg dose. Based on the predictions of exposures following administration of 200, 300, and 400 mg QD in subjects with mild, moderate, and severe hepatic impairment at steady-state, the results and trends observed at 200, 300, and 400 mg QD were similar to those observed after a single dose of 200 mg. In PBPK modelling simulation of elacestrant at 345 mg, the steady state AUC and Cmax were predicted to increase by 2.14- and 1.92-fold, respectively, in subjects with moderate hepatic impairment compared to patients with normal hepatic function. Based on the PBPK model, no dose adjustment is required for subjects with mild hepatic impairment, whereas elacestrant dose should be reduced to 300 and 200 mg QD in subjects with moderate and severe hepatic impairment.

No studies in patients with renal impairment were submitted (see discussion on clinical pharmacology).

Pharmacokinetic interaction studies

Elacestrant as a victim

Elacestrant is mainly metabolized by CYP3A4.

Study RAD1901-110 (with a strong CYP 3A4 inhibitor)

Co-administration of the strong CYP3A4 inhibitor itraconazole (200 mg once daily for 7 days) with Orserdu (172 mg once daily for 7 days) increased elacestrant plasma exposure (AUC_{inf}) and the peak concentration (C_{max}) in healthy subjects 5.3 and 4.4-fold, respectively. Physiologically based pharmacokinetic (PBPK) simulations in cancer patients suggested that the concomitant administration of multiple daily doses of elacestrant 345 mg and itraconazole 200 mg may increase elacestrant steady-state AUC and C_{max} 5.5- and 3.9-fold, respectively, which may increase the risk of adverse reactions. PBPK simulations in cancer patients suggested that concomitant administration of multiple daily doses of elacestrant 345 mg with moderate CYP3A4 inhibitors may increase elacestrant steady-state AUC and C_{max} by 2.3- and 1.9-folds, respectively, with fluconazole (200 mg once daily), and by 3.9- and 3.0-folds, respectively, with erythromycin (500 mg four times a day), which may increase the risk of adverse reaction (see SmPC section 4.5).

Study RAD1901-113 (with a CYP 3A4 inducer)

Co-administration of the strong CYP3A4 inducer rifampicin (600 mg once daily for 7 days) with a single dose of ORSERDU 345 mg decreased elacestrant plasma exposure (AUC_{inf}) and the peak concentration (C_{max}) in healthy subjects by 86% and 73%, respectively, which may decrease elacestrant activity.

PBPK simulations in cancer patients suggested that the concomitant administration of multiple daily doses of elacestrant 345 mg and rifampicin 600 mg may decrease elacestrant steady-state AUC and C_{max} by 84% and 77%, respectively, which may decrease elacestrant activity.

PBPK simulations in cancer patients suggested that the concomitant administration of multiple daily doses of elacestrant 345 mg and the moderate CYP3A4 inducer efavirenz (600 mg) may decrease elacestrant steady-state AUC and C_{max} by 57% and 52%, respectively, which may decrease elacestrant activity.

Study RAD1901-115 (with a PPI)

There was no significant effect on elacestrant exposure when elacestrant was co-administered with omeprazole. Elacestrant Cmax, AUC0–t, and AUC0–∞ geometric least squares mean ratios for elacestrant alone and elacestrant with omeprazole were all close to 1 and the 90% CIs were entirely contained within 0.80 and 1.25.

Elacestrant as a perpetrator

Study RAD1901-114 (with another highly protein bound drug).

Elacestrant Cmax, AUC0–t, and AUC0–∞ geometric least squares mean ratios for elacestrant alone and elacestrant with warfarin were all close to 1 and the 90% CIs were entirely contained within 0.80 and 1.25, and there was no significant effect on R-warfarin exposure when warfarin was co-administered with elacestrant. R-and S-warfarin Cmax, AUC0–t, and AUC0–∞ geometric least squares mean ratios for warfarin alone and warfarin with elacestrant were all close to 1 and the 90% CIs were entirely contained within 0.80 and 1.25.

Study RAD1901-118 (with a p-gp substrate and BCRP substrate)

Digoxin Cmax, AUC0–t, and AUC0–∞ geometric least squares means were higher (27%, 13%, and 10%, respectively) when digoxin was administered with elacestrant compared to when administered alone. The applicant concluded that the digoxin AUC0-∞ 90% CIs of the geometric least squares mean ratio were entirely contained within 0.80 and 1.25, and that for AUC0–t, the upper bound of the 90% CI was > 1.25. Further, the digoxin Cmax 90% CIs of the geometric least squares mean ratio did not contain 1 and the upper bound was > 1.25.

Rosuvastatin Cmax, AUC0–t, and AUC0–∞ geometric least squares means were higher (45%, 23%, and 20%, respectively) when rosuvastatin was administered with elacestrant compared to when rosuvastatin was administered alone. For all 3 rosuvastatin exposure parameters, the upper limit of 90% CI was > 1.25.

PBPK simulations

The applicant simulated mean plasma elacestrant concentrations following single oral doses of 200 or 400 mg elacestrant in the absence of any perpetrator and on the 15th day of 28 days of dosing of itraconazole (200 mg QD, a strong CYP 3A4 inhibitor) / fluconazole (200 mg QD, a moderate CYP 3A4 inhibitor) / erythromycin (500 mg QID, a mechanism-based inhibitor) / cimetidine (400 mg BID, a mild CYP 3A4 inhibitor) to healthy subjects. Based on these simulations, the applicant concluded that co-administration with itraconazole, fluconazole, erythromycin, or cimetidine leads to strong (>5-fold), moderate (>2-fold), moderate (>3-fold), and weak (1.1-fold) inhibition of elacestrant metabolism, respectively.

The model was also used to predict the likely outcome of DDI with efavirenz (moderate CYP3A4 inducer, 600 mg QD) following a single dose of elacestrant 400 or 800 mg. Efavirenz Indmax for CYP3A4 was scaled based on rifampicin Indmax of 8 to be 5.14. Prospective use of the model to predict the likely outcomes of interaction indicated decreases in elacestrant exposure with GMRs for AUC0-336h and Cmax of 0.452 and 0.561 at 400 mg.

2.6.2.2. Pharmacodynamics

Mechanism of action

Elacestrant, a tetrahydronaphthalene compound, is a potent, selective and orally active oestrogen receptor-α (ERα) antagonist and degrader (see SmPC section 5.1).

Primary and Secondary pharmacology

RAD1901-106: A phase 1b study to evaluate the effect of RAD1901 on the availability of oestrogen receptor biding sites in metastatic breast cancer lesions using 16α-^{18}F-fluoro-17β-oestradiol positron emission tomography imaging.

This was a Phase 1b, open-label, non-randomized, multicentre, international, 2 dose cohort study in postmenopausal women with histologically-confirmed, ER+, human epidermal growth factor receptor 2 negative (HER2-) mBC. The study included postmenopausal women 18 years of age or older with histologically-proven ER+, HER2- inoperable and/or mBC, tumour progression after ≥6 months of at least 1 line of hormonal systemic treatment in the metastatic setting, with ECOG performance status 0-2. Subjects had to have had ≤3 lines of endocrine therapy for metastatic disease.

Results

A total of 8 subjects were initially enrolled and treated with 400 mg elacestrant; a second cohort of 8 subjects was subsequently enrolled and treated with 200 mg elacestrant for 14 days, after which the dose was escalated to 400 mg once daily (QD). Elacestrant was dosed QD continuously with 28-day treatment cycles. Fluoroestradiol-positron emission tomography (FES-PET) imaging was conducted at baseline and on Day 14. Response and progression were evaluated using RECIST v1.1 criteria.

The primary endpoint was the percentage difference in Fluoroestradiol (FES) uptake in tumour lesions (up to a maximum of 20 lesions) after 14 days of treatment with elacestrant compared to baseline. Elacestrant reduced FES uptake from baseline to Day 14. Median reduction in FES uptake was 88.0% (range: 59% to 97%), showing target engagement. This reduction in FES uptake was similar in subjects with or without ESR1 mutations (data not shown). All but 1 subject in the 400 mg dose cohort (7/8; 87.5%) and 57% of subjects (4/7) in the 200/400 mg cohort obtained a greater than 75% reduction in FES uptake.

ORR was 11.1% (1/9; partial response), CBR at 24 weeks was 30.8%, duration of response (DoR) was 22 weeks, time to response was 7.9 weeks, and median progression-free survival (PFS) was 5.3 months in the overall population. The single response was observed in the initial 400 mg dose group. No significant correlation was found between FES uptake and best overall response using Spearman's rank correlation coefficient (0.2608 overall; p-value >0.5).

Study 3882-0013: Elacestrant concentration-QTc modelling. QT Evaluation Report.

Available time-matched PK and QT observations were obtained from multiple PK studies in healthy postmenopausal women and men, and from studies in postmenopausal women and men with advanced/metastatic breast cancer (RAD1901-105, RAD1901-106 and RAD1901-308) and used for the elacestrant plasma concentration-QTc analysis. Two PK studies (RAD1901-001 and RAD1901-004) included placebo treatment, all other studies only had screening and pre-dose QTcF observations without elacestrant administration. In addition, all studies had limited ECG sampling apart from studies RAD1901-001 and RAD1901-004 which had intensive ECG sampling. Overall, there was a total of 7016 QT observations from 633 subjects available following placebo and elacestrant treatment for the concentration-QTc analysis. A total of 1863 (27%) were from placebo/pre-dose and 5153 (73%) were from post-initiation of elacestrant treatment.

There was a similar percentage of placebo/pre first elacestrant dose and post first elacestrant dose QTcF observations >450 msec with 2.0% of placebo/pre first elacestrant dose (37 observations) and 2.2% of post first dose QTcF observations (114 observations), respectively. Of the 114 QTcF observations >450 msec post first elacestrant dose, 62 (54%) were from Study RAD1901-005 and QTcF was similar prior to elacestrant and following elacestrant treatment indicating the higher QTcF values in this study were not a result of elacestrant treatment. There were five QTcF observations >480 msec following elacestrant treatment and 1 QTcF observation >500 msec.

There was a similar percentage of placebo and elacestrant dQTcF observations >30 msec (2.4% and 2.2%), respectively and there were only two dQTcF observations >60 msec.

Exploratory plots of dQTcF versus time-matched concentrations of elacestrant did also not indicate QTcF prolongation with increasing concentrations of elacestrant. This was further confirmed by the population concentration-QTcF modelling which showing only a slight positive relationship (p=0.00694) with increasing concentrations of elacestrant.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics of elacestrant is considered overall adequately investigated. Based on low solubility and low permeability elacestrant is considered a BCS class IV drug substance. The low BA of 10% questions the development of an oral immediate-release formulation for elacestrant drug substance which is mainly metabolised by CYP3A4 and prone to be glucuronised and sulfatised at the OH-group.

Initially the applicant proposed that elacestrant could be taken without regard to food based on popPK modelling and disregarding the slightly higher exposure observed with high-fat compared to low-fat meals. However, in the Phase 3 Study RAD1901-308, elacestrant was administered with a light meal and the applicant claimed that improved gastrointestinal tolerability has been observed when tablets were taken with food (study RAD1901-116). Also, variability of all PK parameters was decreased after intake in fed state vs. fasted state which is deemed supportive of a recommendation in fed state to stabilise exposure. Therefore, the product should be recommended to be taken accordingly, i.e. with food.

PK data from 4 studies with capsule formulation (used in early development) had been used in a preliminary popPK. No formulation effect between capsule and tablet formulations was found significant so that similar bioavailability between capsule and final FCT formulation can be concluded.

No dose adjustment seems to be necessary for different age, body weight groups and gender. No studies in patients with renal impairment were submitted (See discussion on clinical pharmacology). Studies in subjects with renal impairment are waived since renal excretion of elacestrant is minimal and creatinine clearance was found to have no effect on elacestrant clearance in the popPK model. The PBPK model is considered adequate to predict elacestrant dose and time-dependent PK and therefore to evaluate the impact of hepatic impairment on pharmacokinetics of elacestrant.

Overall, the Cmax and AUC values were similar between subjects in the mild hepatic impairment group (Child-Pugh A) and the normal hepatic function group upon single dose administration of elacestrant 176 mg. There were significant increases in AUC0–t (76%) and AUC0–∞ (83%) in the moderate hepatic impairment group (Child-Pugh B) compared to the normal hepatic function group. The Cmax values were similar between the normal and moderate impairment groups. The geometric mean elimination half-life (t1/2) tended to increase with increasing severity of hepatic impairment. Elacestrant has not been studied in subjects with severe hepatic impairment (Child-Pugh C) (See SmPC section 5.2).

Based on the PBPK model, no dose adjustment is required for subjects with mild hepatic impairment, whereas elacestrant dose should be reduced to 300 mg for subjects with a moderate hepatic impairment, which is acceptable.

Regarding severe hepatic impairment, since no clinical data is available in this subpopulation, the applicant is recommended to perform a post-approval clinical study to assess the effect of severe hepatic impairment on elacestrant PK in order to provide dose recommendations for this population (REC). The final study report submission is planned in June 2026.

In vitro, elacestrant is a substrate of the hepatic uptake transporter OATP2B1 and thus drug-drug interactions with OATP2B1 inhibitors cannot be excluded. The possible clinical relevance of interactions

between OATP2B1 inhibitors and elacestrant (as a victim) has been included in the product information (See SmPC section 4.5).

The concomitant use of elacestrant with CYP3A4 inhibitors was investigated and the relevance of the design / chosen doses was discussed: for elacestrant, as a drug with dose-dependent PK, a therapeutic dose of 400 mg should have been used instead of 200 mg; for itraconazole, the highest generally recommended dose under therapeutic conditions, i.e. 200 mg bid, should have been used instead of 200 qd. However, the choice of the reduced dose of 200 mg for elacestrant was based on the safety considerations in order to avoid exposing healthy volunteers to unnecessary and unacceptable toxicities. In addition, the dose of 200 mg QD of itraconazole provided sufficient inhibition of CYP3A4 while avoiding an increased potential for adverse events with the drug. Furthermore, the PBPK model was used to simulate mean plasma elacestrant concentrations at steady-state following 200 or 400 mg QD doses in the absence or presence of 200 mg of itraconazole to mimic the clinical situation. Hence, the chosen dose for elacestrant is considered acceptable. Furthermore, considering that trough concentrations had not quite reached its PK steady state by the end of the 7-day coadministration phase for both substances, exposures of the perpetrator itraconazole were sufficiently high for studying the DDI with elacestrant and published literature supported different doses and study designs to adequately study drug interactions with itraconazole.

The proposed dose adjustments regarding concomitant use of strong and moderate CYP3A4 inhibitors were adequately justified, taking into account that the PBPK model was considered acceptable and suitable for conclusions on the integrated DDI/PBPK model strategy performed by the applicant. That no dose adjustments are required for coadministration with mild CYP3A4 inhibitors was also adequately justified by the popPK exposure data from the pivotal study (See SmPC section 4.2).

The concomitant use of elacestrant with CYP3A4 inducers was also investigated. It is unclear from this single-dose study how the effect size of a strong or moderate inducers would affect steady-state treatment exposure. Nevertheless, the PBPK model and the integrated approach proposed to investigate DDI of elacestrant from studies and PBPK is generally accepted. Although no dose adjustments for coadministration with strong and moderate CYP3A4 inducers are proposed, increasing the dose of elacestrant for coadministration with strong or moderate CYP3A4 inducers despite an adequate plasma exposure of elacestrant in terms of efficacy is not recommended because of the increased risk of gastrointestinal adverse events. In addition, if short term or intermittent use of strong or moderate CYP3A4 inducers is necessary, the expected lowering of elacestrant exposure will, in essence, be similar to the exposure associated with elacestrant short term dose reduction because of adverse events. Based on the provided simulations, the duration of concomitant treatment should be reduced to ≤ 3 days for strong CYP3A4 inducers in order to prevent concentrations dropping below the previously described efficacious threshold of 20 ng/mL. Although for moderate CYP3A4 inducers a longer duration might be possible, the duration for the use of moderate inducers should be also ≤ 3 days to avoid confusion for the practitioners (See SmPC section 4.2).

No dose adjustment for concomitant intake with weak CYP 3A4 inducers is considered required. This is based on an exploratory analysis performed using elacestrant final population PK model to derive individual elacestrant steady state PK parameters $C_{max,ss}$, $C_{min,ss}$ and $AUC_{tau,ss}$ based on the observed plasma concentrations for each patient in the Phase III Study RAD1901-308. The comparison of the $C_{max,ss}$, $C_{min,ss}$ and $AUC_{tau,ss}$ distributions for these patients taking weak CYP3A4 inducers compared with patients not taking CYP3A4 inducers did not reveal significant differences. *In vitro*, elacestrant showed a potential for inhibition of the intestinal P-gp and BCRP. Elacestrant is also a highly protein bound drug. The systemic DDI risk for CYP3A4 inhibition by elacestrant is low. Elacestrant is not expected to inhibit CYP3A4 activity at clinically relevant concentrations up to the exposure obtained at the therapeutic dose of 400 mg QD of elacestrant dihydrochloride (345 mg elacestrant). Concomitant use of elacestrant with other P-gp substrates or with other BCRP substrates may increase their

concentrations, which may increase the adverse reactions associated with the P-gp substrates or BCRP substrates. The dose of coadministered P-gp substrates or BCRP should be reduced according to their SmPC.

Primary pharmacology: Study RAD1901-106 (106) was a phase 1b study to evaluate the effect of RAD1901 on the availability of oestrogen receptor binding sites in metastatic breast cancer (mBC) lesions using 16α-^{18}F-fluoro-17β-oestradiol positron emission tomography imaging. PET-FES can be used for whole-body evaluation of tumour ER expression and previous studies showed a reduction in ER availability measured by FES uptake for fulvestrant. (Van Kruchten et al, *Cancer Discovery*, 2015). Study 106 showed that both doses of 400 mg and 200 mg reduced FES uptake in tumour lesions at day 14, indicative of reduced levels of ER expression upon elacestrant treatment and supporting the mechanism of action. However, a lower proportion of patients in the 200/400 mg dose obtained a ≥75% reduction in FES uptake (200 mg minimal recommended dose upon dose reduction due to adverse events). Based on the combined PK and PD results from this study the concentration at which a greater than 75% reduction in FES uptake was observed was geometric mean Cmin at Day 14 (i.e. 20 ng/mL) and this was utilised as the target mean Cmin for target engagement.

With regards to target engagement, while some *in vitro* tests suggested selectivity to mutant ESR1 over wt-ESR1 other pre-clinical tests did not (see non-clinical aspects).

The proposed indication has been narrowed to breast cancer patients with ESR1 mutations. In section 5.1 of the SmPC targeted mutations have been defined as those in the ligand binding domain.

In patients, elacestrant was observed to penetrate the blood-brain barrier in a dose-dependent manner, with median elacestrant total (bound and unbound) concentrations in cerebrospinal fluid of 0.0966 ng/mL for the 200 mg dose group and 0.155 ng/mL for the 500-mg dose group. A weak agonistic activity of elacestrant, i.e. reduction in LH levels, was observed in ovariectomised rats. However, no similar effects were observed in humans. Moreover, elacestrant could exert the effect on LH levels at peripheral (pituitary) rather than at CNS level (hypothalamus). In addition, elacestrant concentrations in patients (considering interindividual variability) will be sufficiently high to elicit the expected antagonistic effect.

Secondary pharmacology: No dedicated QTc study was submitted which is acceptable based on the non-clinical data and that there is no indication of a class-effect based on what is known for fulvestrant. Slight trends toward longer QTcF and toward decreased QTcF change from baseline were observed with increasing elacestrant plasma concentrations. Data suggested that oral elacestrant doses of up to 1000 mg daily (2.5× the anticipated therapeutic dose of 400 mg) did not adversely affect cardiac repolarisation, although there were few data points at higher exposure. Nevertheless, it is considered there is no signal for QTc prolongation based on the totality of data.

Exposure-Response relationship: There was no clear relationship between PFS and elacestrant exposure, as represented by the average daily AUC (AUCav). Logistic regression analysis did not indicate a higher probability of clinical benefit with increasing exposure (AUCav) of elacestrant. The clinical relevance of CBR is however limited as PFS was the primary endpoint of the phase 3 study.

Exposure-Safety relationship: Logistic regression analysis did not indicate a higher probability of first occurrence of nausea with increasing exposure (Conc4h) of elacestrant. The odds ratio and associated 95% CI for Conc4h included the null value of 1 and the p-value was not statistically significant ($p<0.001$). However, the exposure response analysis is limited as majority of patients received 400 mg.

In the initial exposure-safety response analysis (MENA-PMX-RAD1901-3863), the number of subjects was very limited, i.e. 32 with only 5 subjects displaying any drug-related AE. Mean AUC, Cave, Cmin,

and Cmax of RAD1901 in patients with "All AEs" were 52-65% higher than those without AEs. Considering a very low number of subjects included, the results should be interpreted with caution.

In the final exposure response analysis, the nominal steady state AUC(0-24) for the patients in Study RAD1901-308 were overlaid on the logistic curves of (i) the probability of clinical benefit rate and overall response vs AUC and (ii) the probability SAE, Grade 3 AEs and AEs leading to study discontinuation vs AUC obtained in a preliminary analysis based on efficacy and safety data from Phase 1 studies RAD1901-005 and RAD1901-106. The probability of experiencing any type of severe AEs increased for doses higher than 400 mg QD, while in the range of exposures observed in Phase 3 RAD1901-308 study this probability did not increase markedly, remaining below 50%. The probability of clinical benefit (CB) and OR seems to be decreasing with a higher AUC, which is not explained (see 2.6.6. clinical efficacy discussion, for a more detailed discussion).

2.6.4. Conclusions on clinical pharmacology

Elacestrant is a SERD that can be orally administered. Doses of 400 mg and, to a lesser extent, 200 mg reduced FES uptake in tumour lesions after 14 days of treatment, indicative of reduced levels of ER expression upon elacestrant treatment and supporting the mechanism of action. The proposed indication was narrowed to patients with ESR1 mutations, which is endorsed.

There was no clear relationship between PFS and elacestrant exposure. Logistic regression analysis did not indicate a higher probability of first occurrence of nausea with increasing exposure (Conc4h) of elacestrant; however, modelling for other AEs suggest a positive exposure-correlation.

The CHMP recommended to perform a clinical PK study in non-cancer patients to evaluate the effect of severe hepatic impairment on elacestrant pharmacokinetics to provide dose recommendations in this patient group (REC). Final report expected: June 2026.

2.6.5. Clinical efficacy

Elacestrant has been evaluated for efficacy in 2 Phase 1 studies and a randomized Phase 3 pivotal study (Table 19). The results from these studies informed the selection of the recommended elacestrant dose and the design of the subsequent Phase 3 Study RAD1901-308 (see Table 19).

The recommended dose is 345 mg (one 345 mg film-coated tablet), once daily, with food. The quantitative declaration of active moiety corresponding to 400 mg of the elacestrant dihydrochloride salt is 345.13 mg of elacestrant free base. Therefore, the posology of 400 mg will be referred to in the rest of the report.

2.6.5.1. Dose response study(ies)

Study RAD1901-005: A phase 1, multicentre, open-label, multipart, dose-escalation study of RAD1901 in postmenopausal women with advanced oestrogen receptor positive and HER2-negative breast cancer.

Study design

This was a Phase 1, multicentre, open-label, multi-part, dose-escalation study to determine the Maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of elacestrant in subjects

with ER+/HER2- mBC. Secondary objectives included evaluating the PK of elacestrant and an exploratory assessment of pharmacodynamics.

The study consisted of 4 parts:

- Part A: to evaluate the safety and tolerability, PK, and preliminary anti-tumour efficacy of elacestrant in a 3 + 3 dose-escalation phase using capsules
- Part B: a safety expansion phase at the RP2D using capsules
- Part C: to evaluate the tablet formulation administered at the RP2D
- Part D: to evaluate the safety and tolerability, PK, and preliminary anti-tumour efficacy of elacestrant tablet formulation at the RP2D of 400 mg QD in a population of subjects with more homogeneous anticancer therapies.

Parts A, B, and C included postmenopausal women with ER+/HER2- mBC who had received 2 or fewer chemotherapy regimens with progression after at least 6 months of endocrine therapy. Part D included postmenopausal women with ER+/HER2- mBC with at least 2 lines of prior endocrine therapy, including prior fulvestrant and prior treatment with a cyclin-dependent kinase (CDK) 4/6 inhibitor.

Subjects in Part A were treated with elacestrant 200 mg QD, 400 mg QD, or 600 mg QD. All subjects in Parts B, C, and D were treated with 400 mg QD. Upon confirmation of the RP2D (400 mg QD), subjects enrolled at lower doses in Part A were permitted to have their dose escalated to RP2D. The study was terminated prior to completion of enrolment of the Part D cohort due to a change in corporate strategy. Treatment cycles were of 28 days per cycle.

Results

The RP2D was determined to be 400 mg QD. Of 57 postmenopausal women enrolled, 50 received the RP2D (400 mg QD: 26 capsules, 24 tablets). Median age was 63 years, median 3 prior anticancer therapies including CDK4/6 inhibitors (52.0%), SERD (52.0%), and *ESR1* mutation (circulating tumour DNA; 50.0%). No dose-limiting toxicities occurred; the most common adverse events at RP2D (400 mg tablet; n = 24) were nausea (33.3%) and increased blood triglycerides and decreased blood phosphorus (25.0% each). Most adverse events were Grade 1 to 2 in severity. Although no dose-limiting toxicities were reported per-protocol, the 600 mg dose was deemed not tolerable due primarily to gastrointestinal events. The incidence of nausea, vomiting, and constipation was higher in subjects who received the 600 mg dose (67% to 100%) compared with those who received the 400 mg dose (17% to 65%). The 400 mg dose, which was associated with fewer gastrointestinal events, was selected as the RP2D for the subsequent clinical studies. An overall summary of adverse events (Table 21) and the incidence of gastro-intestinal events (Table 22) are shown below.

Table 21: Overall summary of adverse events in Study 005

Adverse Event Category	Elacestrant 200 mg Capsule (N=4) n (%)	Elacestrant 400 mg Capsule (N=26) n (%)	Elacestrant 600 mg Capsule (N=3) n (%)	Elacestrant 400 mg Tablet (N=24) n (%)	Elacestrant All 400 mg (N=50) n (%)	Overall (N=57) n (%)
Any TEAEs	4 (100)	26 (100)	3 (100)	22 (91.7)	48 (96.0)	55 (96.5)
Any Treatment-Related TEAEs	4 (100)	25 (96.2)	3 (100)	19 (79.2)	44 (88.0)	51 (89.5)
Any Serious TEAEs	1 (25.0)	5 (19.2)	1 (33.3)	8 (33.3)	13 (26.0)	15 (26.3)
Any Treatment-Related Serious TEAEs	1 (25.0)	0	0	1 (4.2)	1 (2.0)	2 (3.5)
Any Grade 3 or 4 TEAEs	1 (25.0)	12 (46.2)	1 (33.3)	10 (41.7)	22 (44.0)	24 (42.1)
Any Treatment-Related Grade 3 or 4 TEAEs	1 (25.0)	6 (23.1)	1 (33.3)	1 (4.2)	7 (14.0)	9 (15.8)
Any TEAEs Requiring Dose Interruption	0	8 (30.8)	1 (33.3)	8 (33.3)	16 (32.0)	17 (29.8)
Any TEAEs with Outcome of Death	0	1 (3.8)	1 (33.3)	1 (4.2)	2 (4.0)	3 (5.3)
Any TEAEs Leading to Discontinuation of Study Medication	0	5 (19.2)	0	1 (4.2)	6 (12.0)	6 (10.5)
Any Treatment-Related TEAEs Leading to Discontinuation of Study Medication	0	5 (19.2)	0	0	5 (10.0)	5 (8.8)

Abbreviations: ITT = intent-to-treat; TEAE = treatment emergent adverse event
Study RAD1901-005 database lock date: December 20, 2019.

Table 22: Frequently reported (≥10%) gastrointestinal TEAEs in Study 005

Adverse Event	Elacestrant 200 mg Capsule (N=4) n (%)	Elacestrant 400 mg Capsule (N=26) n (%)	Elacestrant 600 mg Capsule (N=3) n (%)	Elacestrant 400 mg Tablet (N=24) n (%)	Elacestrant All 400 mg (N=50) n (%)	Overall (N=57) n (%)
At Least 1 TEAE	4 (100)	26 (100)	3 (100)	22 (91.7)	48 (96.0)	55 (96.5)
Gastrointestinal disorders	3 (75.0)	24 (92.3)	3 (100)	19 (79.2)	43 (86.0)	49 (86.0)
Nausea	1 (25.0)	17 (65.4)	3 (100)	8 (33.3)	25 (50.0)	29 (50.9)
Dyspepsia	2 (50.0)	11 (42.3)	1 (33.3)	5 (20.8)	16 (32.0)	19 (33.3)
Vomiting	0	11 (42.3)	3 (100)	4 (16.7)	15 (30.0)	18 (31.6)
Constipation	1 (25.0)	5 (19.2)	2 (66.7)	5 (20.8)	10 (20.0)	13 (22.8)
Diarrhoea	1 (25.0)	9 (34.6)	0	3 (12.5)	12 (24.0)	13 (22.8)
Gastrooesophageal reflux disease	0	7 (26.9)	1 (33.3)	2 (8.3)	9 (18.0)	10 (17.5)
Flatulence	1 (25.0)	6 (23.1)	1 (33.3)	1 (4.2)	7 (14.0)	9 (15.8)
Abdominal pain	1 (25.0)	3 (11.5)	0	2 (8.3)	5 (10.0)	6 (10.5)

The objective response rate (ORR) was 19.4% (n = 31 evaluable subjects receiving the RP2D), 15.0% in subjects with prior SERD (n = 3 out of 20), 16.7% in subjects with prior CDK4/6 inhibitor (n = 3 out of 18), and 33.3% in subjects with *ESR1* mutation (n = 5 out of 15).

RAD1901-106: A phase 1b study to evaluate the effect of RAD1901 on the availability of oestrogen receptor biding sites in metastatic breast cancer lesions using 16α-18F-fluoro-17β-oestradiol positron emission tomography imaging.

This study is discussed in the section Primary Pharmacology (See 2.6.2.).

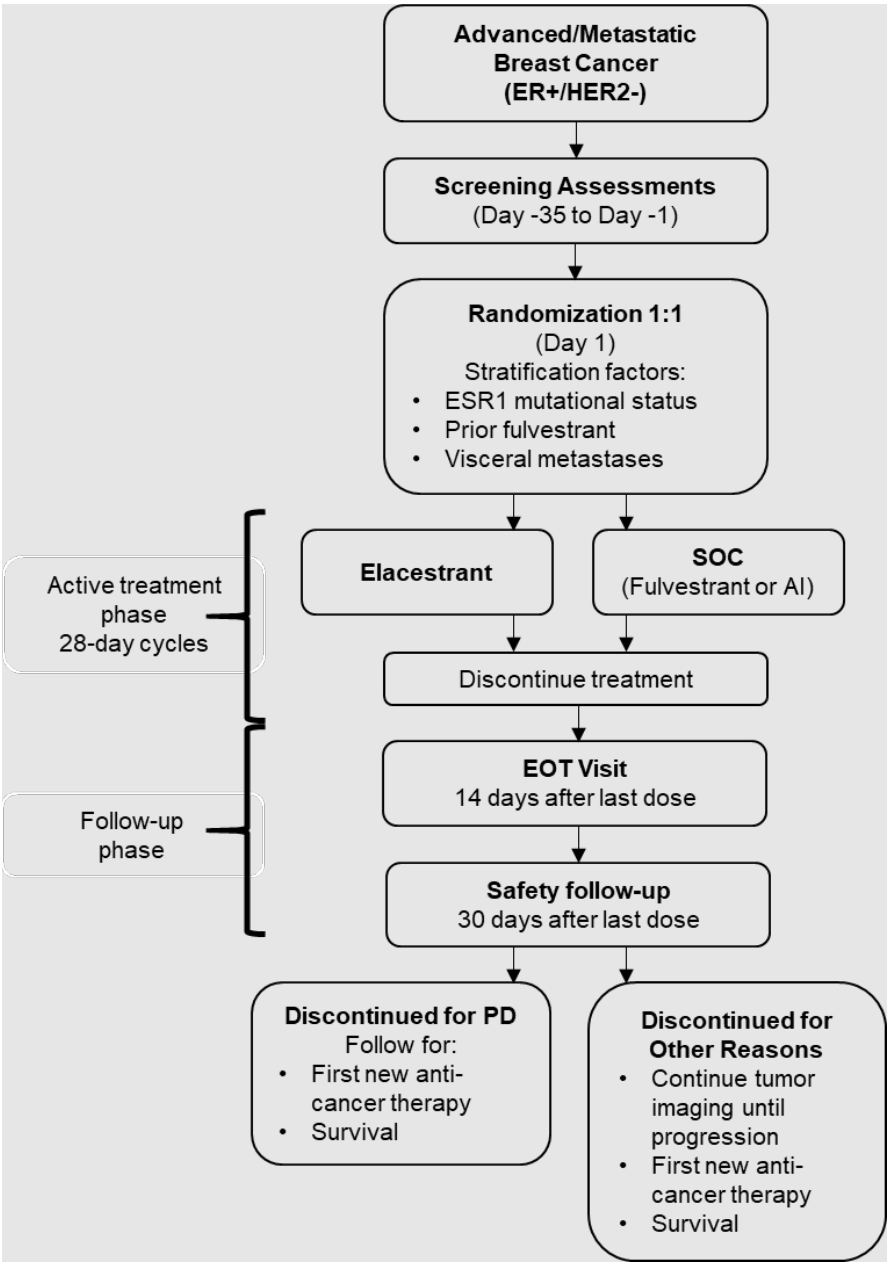
2.6.5.2. Main study(ies)

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, multicentre trial (EMERALD)

Methods

Study 308 (Figure 8) was an international, multisite, randomized, open-label, active-controlled, event-driven, Phase 3 clinical study comparing the efficacy and safety of elacestrant versus standard of care (SOC) therapy (fulvestrant or AI) in postmenopausal women and men with ER+/HER2- mBC whose disease has relapsed or progressed on at least 1 and no more than 2 prior lines of endocrine therapy for mBC, which must have included CDK4/6i therapy in combination with fulvestrant or an AI. Subjects must have received no more than 1 line of cytotoxic chemotherapy for mBC. Endocrine monotherapy with 1 of the SOC drug options (fulvestrant, anastrozole, letrozole, exemestane) must have been an appropriate treatment option for subjects enrolled in this study.

Figure 8: Study design (Study 308)



Abbreviations: AI = aromatase inhibitor; EOT = end of treatment; ER+ = oestrogen receptor positive; *ESR1* = oestrogen receptor gene 1; HER2- = human epidermal growth factor receptor 2 negative; PD = progressive disease; SOC = standard of care.
Source: Study 308, Figure 1

- **Study Participants**

Inclusion criteria

1. Must have had a histologically- or cytologically-proven diagnosis of adenocarcinoma of the breast with evidence of either locally advanced disease not amenable to resection or radiation therapy with curative intent or metastatic disease not amenable to curative therapy
2. Must have been appropriate candidates for endocrine monotherapy
3. Must have had 1 of the following as defined by RECIST version 1.1:
   a. Measurable disease

b. Bone only disease with evaluable lesions. Subjects must have had at least 1 lytic or mixed lytic/blastic bone lesion; blastic lesions only are not evaluable and were not allowed. Subjects who had prior radiation to bone must have at least 1 evaluable lesion in a nonirradiated area

4. Female or male ≥ 18 years of age
5. Female subjects must have been postmenopausal women, defined by 1 of the following criteria:
   a. Documented bilateral surgical oophorectomy
   b. Age ≥ 60 years with amenorrhea ≥ 1 year since last menses
   c. Age < 60 years with amenorrhea ≥ 1 year since last menses with no alternative pathological or physiological cause (including ongoing or recent chemotherapy, treatment with tamoxifen or toremifene, or a gonadotropin releasing hormone (GnRH) agonist), and serum oestradiol and follicle stimulating hormone (FSH) levels within the laboratory reference range for postmenopausal women
   d. Age < 60 years with tamoxifen or toremifene therapy within the last 12 months, with documentation of 12 months of amenorrhea prior to tamoxifen or toremifene therapy and serum oestradiol and FSH levels within the laboratory reference range for postmenopausal women
   e. Females with hormonally-induced menopause (i.e., requiring ongoing hormone suppression) were not eligible
6. Male subjects had to, even if surgically sterilized (i.e., status post-vasectomy):
   a. Agree to practice highly effective barrier contraception (use condoms) during the entire study treatment period and through 120 days after the last dose of study drug. For subjects (who have not undergone vasectomy) with female partners of childbearing potential, the subject and his partner must have, in addition to condoms, used highly effective contraceptive measures when engaging in sexual intercourse throughout the treatment period and for at least 120 days after the last dose of study drug
      OR
      Agree to practice true abstinence during the entire study treatment period and through 120 days after the last dose of study drug
      Note: Abstinence was only to be used as a contraceptive method if in line with the subject's usual and preferred lifestyle. Periodic abstinence was not an acceptable method of contraception.
   b. Agree not to donate sperm during the course of treatment period of this study or within 120 days after receiving the last dose of the study drug
7. Must have had ER+ and HER2- tumour status confirmed per local laboratory testing. Status may have been confirmed on original diagnosis tissue samples or post-treatment (PTx) samples (most recent biopsy preferred, if testing available). ER and HER2 testing was to be performed in the following manner:
   a. Documentation of ER+ tumour with ≥ 1% staining by immunohistochemistry (IHC) as defined in the 2010 American Society of Clinical Oncology (ASCO) recommendations for ER testing (Hammond et al, 2010), with or without progesterone receptor positivity
      AND
   b. Documentation of HER2- tumour with an IHC result of 0 or 1+ for cellular membrane protein expression or an in situ hybridisation negative result as defined in the 2013 or 2018 ASCO recommendations for HER2 testing (Wolff et al, 2013; Wolff et al, 2018).
8. Must have previously received at least 1 and no more than 2 lines of endocrine therapy, either as monotherapy or as a combination therapy with another agent, for mBC:
   a. Must have progressed during or within 28 days of completion of each line of endocrine therapy; i.e., if a subject was discontinued due to toxicity without progression, this would not count as a line of prior therapy

b. For subjects who progressed during or within 12 months of adjuvant endocrine therapy, this will count as 1 line of endocrine therapy for mBC. In the absence of such progression, adjuvant therapy does not count as 1 of the required lines of endocrine therapy

9. Must have progressed during or within 28 days of completion of prior treatment with a CDK4/6i in combination with either fulvestrant or an AI (this counts as a line of prior endocrine therapy) for mBC:
    1. Prior treatment with a CDK4/6i not in combination with fulvestrant or an AI would not fulfil this criterion
    2. Discontinuation of prior CDK4/6i due to toxicity, in the absence of progression, would not fulfil this criterion
10. Must have received no more than 1 line of cytotoxic chemotherapy in the advanced/metastatic setting:
    a. Cytotoxic chemotherapy does not include: CDK4/6is, mechanistic target of rapamycin inhibitors, PI3K inhibitors, or immunotherapy. There are no restrictions on prior use of these agents
    b. There is no requirement for documentation of progressive disease (PD) to prior chemotherapy
    c. Chemotherapy given in combination with endocrine therapy counts as both a line of endocrine therapy and a line of chemotherapy.
    d. Chemotherapy administered for less than 1 cycle will not be counted as a prior line of chemotherapy
    e. For subjects who progress within 12 months of neoadjuvant or adjuvant chemotherapy, this will count as 1 prior line of therapy for advanced/metastatic disease
11. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
12. Resolution of all toxic effects of prior therapies or surgical procedures to Grade ≤ 1 (except alopecia and peripheral neuropathy)
13. Adequate organ function as defined below:
    a. Hematologic function (in the absence of transfusion of red blood cells or platelets or the use of growth factors within the preceding 4 weeks)
    −Absolute neutrophil count ≥ 1.0×10^9/L
    −Platelet count ≥ 75×10^9/L
    −Haemoglobin ≥ 9.0 g/dL
    b. Renal function
    −Estimated glomerular filtration rate ≥ 30 mL/min/1.73 m2 or creatinine clearance calculated by Cockcroft-Gault equation ≥ 30 mL/min
    c. Hepatic function
    −Alanine aminotransferase (ALT) ≤ 3 × upper limit of normal (ULN)
    −Aspartate aminotransferase (AST) ≤ 3 × ULN
    −Total bilirubin ≤ ULN or total bilirubin ≤ 1.5 × ULN with direct bilirubin ≤ ULN of the laboratory in subjects with documented Gilbert's Syndrome
    d. Chemistry
    −Potassium, sodium, calcium (corrected for albumin), magnesium, and phosphorus National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE) version 5.0 Grade ≤ 1. If Screening assessments are abnormal, chemistry assessments may be repeated up to 2 times; subjects may receive appropriate supplementation or treatment prior to reassessment.
    e. Coagulation
    −International normalized ratio (INR) ≤ 1.5
    Note: Subjects who are receiving anticoagulation treatment which is monitored by INR may be allowed to participate if they have a stable INR (i.e., within therapeutic range) for at least 28 days prior to the first dose of study drug, in the absence of any exclusionary medical conditions, and provided that an AI would be appropriate therapy for the subject.

14. Ability to understand the protocol and provide informed consent

Exclusion criteria

1. Prior treatment with elacestrant or investigational SERD or ER antagonist
2. Prior anticancer or investigational drug treatment within the following windows:
   a. Fulvestrant treatment (last injection) < 42 days before first dose of study drug
   b. Any other endocrine therapy < 14 days before first dose of study drug
   c. Chemotherapy or other anticancer therapy < 21 days before first dose of study drug
   d. Any investigational anticancer drug therapy < 28 days or 5 half-lives (whichever is shorter) before the first dose of study drug. Enrolment of subjects whose most recent therapy was an investigational agent was to be discussed with Radius
   e. Bisphosphonates or RANKL inhibitors initiated or dose changed < 3 months prior to first dose of study drug
3. Radiation therapy within 14 days (28 days for brain lesions per Exclusion Criterion 4) before the first dose of study drug
4. Presence of symptomatic metastatic visceral disease, including but not limited to, extensive hepatic involvement, untreated or progressive central nervous system (CNS) metastases, or symptomatic pulmonary lymphangitic spread. Subjects with discrete pulmonary parenchymal metastases were eligible provided their respiratory function was not significantly compromised as a result of disease in the opinion of the investigator. Subjects with previously treated CNS metastases were eligible provided that all known lesions were previously treated, they had completed radiotherapy at least 28 days prior to first dose of study drug and were clinically stable. If anticonvulsant medication was required, subjects were to be stable on a non-enzyme inducing anticonvulsant regimen
5. Intact uterus with a history of endometrial intraepithelial neoplasia (atypical endometrial hyperplasia or higher-grade lesion)
6. Diagnosis of any other malignancy within 5 years before enrolment, except for adequately treated basal cell or squamous cell skin cancer, carcinoma in situ of the cervix, or second primary breast cancer
7. Any of the following within 6 months before enrolment: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of NCI CTCAE version 5.0 Grade ≥ 2, prolonged total depolarisation and repolarisation time (QT) corrected by Fridericia's formula (QTcF) ≥ Grade 2 (i.e., > 480 msec), uncontrolled atrial fibrillation of any grade, coronary/peripheral artery bypass graft, heart failure ≥ Class II as defined by the New York Heart Association guidelines, or cerebrovascular accident including transient ischemic attack
8. Child-Pugh Score greater than Class A (i.e., score > 6)
9. Coagulopathy or any history of coagulopathy within the past 6 months, including history of deep vein thrombosis or pulmonary embolism. However, subjects with the following conditions were allowed to participate:

   Adequately treated catheter-related venous thrombosis occurring > 28 days prior to the first dose of study drug

   Treatment with an anticoagulant for a thrombotic event occurring > 6 months before enrolment, or for an otherwise stable and allowed medical condition, provided dose and coagulation parameters (as defined by local SOC) are stable for at least 28 days prior to the first dose of study drug and provided that an AI would be an appropriate therapy for the subject
10. Known bleeding disorder which, in the opinion of the investigator, would prohibit administration of fulvestrant if that would be the SOC choice for the subject
11. Known difficulty in tolerating oral medications or conditions which would impair absorption of oral medications such as: uncontrolled nausea or vomiting (i.e., CTCAE ≥ Grade 3 despite antiemetic

therapy), ongoing gastrointestinal obstruction/motility disorder, malabsorption syndrome, or prior gastric bypass

12. Unable or unwilling to avoid prescription medications, over-the-counter medications, dietary/herbal supplements, and/or foods that are moderate/strong inhibitors or inducers of CYP3A4 activity. Participation was allowed if the medication, supplements, and/or foods were discontinued for at least 5 half-lives or 14 days (whichever is longer) prior to study entry and for the duration of the study
13. Major surgery < 28 days before the first dose of study drug
14. Any concurrent severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with compliance with study procedures or the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study
15. Known hypersensitivity reaction to drugs chemically related to elacestrant or their excipients
16. Known hypersensitivity to fulvestrant, anastrozole, letrozole, or exemestane (or to any of their excipients), unless treatment with 1 of the other 3 of these 4 treatment options would be appropriate therapy
    Subjects who met any contraindication, according to the respective PI or Summary of Product Characteristics (SmPC), for any SOC drug that the investigator would choose for that subject should the subject be randomized to the SOC group

ESR1 mutation status assessment

Blood samples for circulating tumour deoxyribonucleic acid (ctDNA) analysis were analysed using the Food and Drug Administration (FDA)-approved Guardant360 (Guardant Health) assay to determine *ESR1* mutational status. The Guardant360 assay uses digital sequencing technology to detect all missense nucleotide variants within the ligand-binding domain of the *ESR1* gene. Detection of any *ESR1* mutation(s), as defined by Guardant Health for the assay, was reported as *ESR1* mutation present (i.e., *ESR1*-mut) (see section 2.6.5.4. . The designation of 'No *ESR1* mutation detected' (*ESR1*-mut-nd) was assigned if there was no mutation present in the *ESR1* gene (i.e., wild-type) or if the mutation status is unknown (ESR1 mutations outside biomarker definition). *ESR1* test results were used for stratification at randomisation; however, the site was not provided with a subject's mutational status during the subject's active treatment phase, unless otherwise required by regulation. Results were provided to sites semi-blinded (i.e., coded as Group A or Group B) for randomisation.

- **Treatments**

For subjects randomized to the control group, the investigator was to select 1 of the available SOC options based on the individual subject's prior treatment history and the investigator's judgment. Sites were required to select the investigator's choice of the control arm during the Screening Phase. This was entered into the Integrated Response Technology (IRT) system by the Investigator at the screening visit prior to randomisation.

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

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

The investigator was to select 1 of the available SOC options according to what was appropriate based on the individual subject's prior treatment history and the investigator's judgment, considering the following general guidance:

- Subjects who had not previously received fulvestrant should be treated with fulvestrant (unless there was a known contraindication).
- Subjects who progressed on prior fulvestrant should be treated with an AI.
- The selection of an AI should be based on prior AI therapy and any known contraindications, as follows:
  - If the subject had previously progressed on a nonsteroidal AI (anastrozole or letrozole) but not received exemestane, the preferred option would be exemestane.
  - If the subject had previously progressed on exemestane but not received a nonsteroidal AI, the preferred option would be a nonsteroidal AI.

For subjects randomized to the elacestrant group, 400-mg tablets were administered orally QD by the subjects on an outpatient basis and at study visits.

Dose reductions of elacestrant due to adverse events were allowed in this study. Dose levels could be reduced to 300 mg QD (3 × 100 mg tablets) and, subsequently, to 200 mg QD (2 × 100 mg tablets) representing 25% and 50% dose reductions from the 400 mg QD starting dose, respectively. Dose reductions below 200 mg QD were not allowed and, if required in the opinion of the Investigator, the subject was to discontinue treatment. Once a dose has been reduced, it could not be re-escalated. No dose escalations above the starting dose of 400 mg QD were permitted.

Dose reductions for subjects receiving AIs were not allowed, as per the prescribing information of these drugs. Dose reductions for subjects receiving fulvestrant were permitted for subjects who developed moderate hepatic impairment (Child-Pugh class B) if deemed unrelated to study drug or disease progression, for whom the dose of fulvestrant should be reduced to 250 mg.

Dose interruptions of elacestrant and SOC treatment of ≤14 consecutive days were permitted. A dose interruption of >14 consecutive days required discussion with the Sponsor prior to resuming study treatment. For all subjects, 1 treatment cycle was 28 days.

Crossover from any treatment group or therapy to another was not allowed while participating in the study.

- **Objectives**

The primary objective of the study was to demonstrate that elacestrant, compared with SOC (fulvestrant or AI), is superior in prolonging PFS based on blinded IRC assessment in postmenopausal women and men with ER+/HER2- mBC, either in *ESR1*-mut subjects or in all subjects (*ESR1*-mut + *ESR1*-mut-nd). The key secondary objective was to compare OS between treatment groups in *ESR1*-mut subjects and in all subjects (*ESR1*-mut + *ESR1*-mut-nd).

- **Outcomes/endpoints**

Definition of endpoints

Progression free survival (PFS) was defined as the time from the date of randomisation until the date of objective disease progression or death (by any cause in the absence of progression).

Overall survival (OS) was defined as the time from the date of randomisation until death due to any cause.

IRC-assessed ORR was defined as the percentage of subjects whose best overall response (BOR) was either CR or PR, where BOR was derived using blinded IRC assessment following the RECIST v1.1 criteria. For each subject, BOR could be 1 and only 1 of the following: CR, PR, SD, PD, and not evaluable (NE), with derivation using the order of CR > PR > SD > PD > NE. Additionally, the response of CR or PR required confirmation at least 4 weeks after the initial documentation of the response.

Duration of response (DoR) was defined as the duration from the first response until disease progression or death from any cause.

Clinical benefit rate (CBR) was defined as the proportion of subjects who had confirmed complete response (CR) or partial response (PR) any time during the study or stable disease (SD) that lasted at least 24 weeks (including disease assessments performed up to a week earlier than the scheduled date).

Primary endpoints

The primary endpoints of the study were:

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

In order to control the family-wise Type I error rate, the truncated Hochberg procedure was used. The selection of this procedure allowed for alpha to pass along from the analyses of the primary endpoint of PFS to the analyses of the key secondary endpoint of OS (Dmitrienko *et al* 2011, Hochberg 1988).

Key secondary endpoints

The key secondary endpoints of the study were:

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

Other secondary endpoints

The following endpoints were analysed for *ESR1*-mut-nd subjects:

- IRC-assessed PFS
- OS

The following endpoints were analysed for *ESR1*-mut subjects, *ESR1*-mut-nd subjects, and all subjects (*ESR1*-mut + *ESR1*-mut-nd):

- Local investigator-assessed PFS
- IRC-assessed ORR
- IRC-assessed duration of response (DoR)
- IRC-assessed clinical benefit rate (CBR)

- Local investigator-assessed ORR
- Local investigator-assessed DoR
- Local investigator-assessed CBR

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

- Safety and tolerability: AEs, SAEs, dose modifications, clinical laboratory parameters (i.e., haematology, chemistry, and coagulation), ECGs, ECOG performance status, and vital signs
- Pharmacokinetics: Evaluation of elacestrant concentrations at predose (pretreatment) and 4 hours postdose on Cycle 1 Day 1 (C1D1), predose (trough concentration [Ctrough]) and 4 hours postdose on C1D15, and predose (Ctrough) on C2D1
- Patient-reported outcome endpoints: Assessed using the HRQOL scales EQ-5D-5L, EORTC QLQ-C30, and PRO-CTCAE

Exploratory endpoints

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

- To determine the difference between treatment groups in time to chemotherapy, defined as the number of days from randomisation to initiation of chemotherapy
- To evaluate alterations in ctDNA relevant to ER+ breast cancer and the CDK4/6 pathway and to explore the relationship between these findings and clinical response
- To characterize alterations in tumour-specific genes, proteins, and RNAs related to oncogenic pathways and proliferation and cell cycle markers in tumour tissue and the relationship between these findings and clinical response.

Efficacy assessments

Tumour assessments were performed every 8 weeks (± 7 days) from the date of randomisation during the active treatment phase of the study and assessed per RECIST v1.1. PROs were also assessed in conjunction with tumour assessments.

Subjects with bone lesions identified by radionuclide bone scan or whole-body magnetic resonance imaging (MRI) at baseline underwent repeat bone scans or whole-body MRI performed every 24 weeks (± 7 days) from the date of randomisation and at the time of confirmation of a complete response (CR). All assessments were to be performed as scheduled at the required intervals according to the Schedule of Assessments, regardless of any dosing delay, to prevent the introduction of bias into the assessment of efficacy.

Tumour assessments, including standardized photography of superficial lesions, were to be performed until radiographically and/or clinically documented (i.e., for photographed or palpable lesions) disease progression per RECIST v1.1, initiation of new anticancer therapy, or discontinuation from overall study participation, whichever occurred first.

Subjects who discontinued study treatment for reasons other than radiographically and/or clinically documented disease progression, per RECIST v1.1, were to continue to have tumour assessments performed every 8 weeks (± 7 days) in the follow-up period, and bone scans or whole-body MRI (as

applicable) as clinically indicated and/or every 24 weeks (± 7 days) until RECIST-defined disease progression, initiation of the first new anticancer therapy, or discontinuation from overall study participation (e.g., death, withdrawal of consent, or loss to follow-up), whichever occurred first. Subjects no longer undergoing tumour assessments were to continue to be monitored every 8 weeks for survival and for the initiation of the first new anticancer therapy. The follow-up period was to conclude at the time of the final OS analysis when approximately 50% of subjects in the study have died.

- **Sample size**

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

Among the *ESR1*-mut subjects, the study required approximately 160 PFS events to have a power of 80% to detect a hazard ratio (HR) of 0.610 at the 2-sided alpha level of 2.5%. The sample size estimate assumed a median PFS of 5.3 months for the SOC treatment group and 8.7 months for the elacestrant treatment group, an increase of approximately 3.4 months among the *ESR1*-mut subjects.

The assumption of median PFS of 5.3 months for the SOC treatment group was based on available data at that time related to the efficacy of fulvestrant as a second/third line treatment in the following pivotal clinical trials:

- EFECT (Chia et al, *Journal of Clinical Oncology*, 2008): Fulvestrant was administered at a dose of 500 mg on Day 0, 250 mg on Days 14 and 28, and 250 mg monthly thereafter. Median PFS on fulvestrant monotherapy: 3.7 months.
- BELLE-2 (Baselga et al, *Lancet Oncology*, 2017): Fulvestrant was administered at a dose of 500 mg on Days 1 and 15 of Cycle 1, and on Day 1 of subsequent 28-day cycles. Median PFS on fulvestrant monotherapy: 5.0 months.
- PALOMA-03 (Cristofanilli et al, *Lancet Oncology*, 2016): Fulvestrant was administered at a dose of 500 mg on Days 1 and 15 of Cycle 1, and on Day 1 of subsequent 28-day cycles. Median PFS on fulvestrant monotherapy: 4.6 months.

Among all subjects (*ESR1*-mut + *ESR1*-mut-nd), a total of approximately 340 PFS events had 92% power to detect a HR of 0.667 at the 2-sided alpha level of 2.5%. The 2-sided alpha level of 2.5% for sample size calculation was selected to ensure that at least 1 of the 2 primary efficacy endpoints would pass the Hochberg procedure to control the overall alpha level at 5.0%.

Among all subjects (*ESR1*-mut and *ESR1*-mut-nd), the study was to have 60% power to detect a hazard ratio of 0.75 for OS at a 1-sided alpha level of 2.5%. Assuming a median OS of 25 months for the SOC treatment group, this 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.

Approximately 114 OS events were expected among the *ESR1*-mut subjects at the time of the second analysis of OS. With 114 OS events, the study was to 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.

- **Randomisation and Blinding (masking)**

Eligible subjects were randomized in a 1:1 ratio to either elacestrant or SOC with randomisation stratified by the following:

- *ESR1* mutation status (detected [*ESR1*-mut] vs not detected [*ESR1*-mut-nd])
- Prior treatment with fulvestrant (yes vs no)
- Presence of visceral metastases (yes vs no); visceral includes lung, liver, brain, pleural, and peritoneal involvement

Given the role of *ESR1* mutations in endocrine resistance (Chandarlapaty et al, *JAMA Oncology*, 2016; Dustin et al*, Cancer*, 2019; Nardone et al, *The Breast*, 2015; O'Leary et al, *Cancer Discovery*, 2018), *ESR1* mutation status was selected as one of the stratification factors, and the trial was powered to detect significant improvements in PFS in this group of patients. The decision to include prior therapy with fulvestrant (yes vs no) was taken as elacestrant shares a similar mechanism of action to fulvestrant (i.e., ER degradation). Presence of visceral metastases is recognized to be associated with poor prognosis and poor clinical outcome.

This was an open-label study as one of the study treatment options was administered via IM injections; thus, study subjects and investigators were not blinded to treatment assignment. To minimize bias in study conduct, personnel performing statistical analyses, including biostatisticians and programmers, were blinded to treatment assignments and aggregated data by treatment assignment until after database lock. Contract research organisation study team members and select Sponsor team members were not blinded to an individual subject's treatment assignment during the conduct of the study but were blinded to aggregated data by treatment assignment until after database lock.

At the time of study conduct, Radius was the sponsor. Parexel was the CRO in charge of study conduct and data management activities and Cytel was the CRO responsible for the statistical analysis. The process of managing access to treatment information was documented in a blind Management Plan (final version dated 01 February 2021). An independent central Imaging Review Committee (IRC), blinded to subjects' treatment assignments, reviewed radiographic images and clinical information collected on-study to determine the endpoints of disease response and progression.

Unblinded safety and efficacy data based on local investigator and IRC assessment and OS were reviewed at prespecified intervals by the IDMC. An unblinded statistician at the contract research organisation performed all analyses in preparation for the IDMC evaluations.

Potential risks of the open-label study design were recognized during the design of the study, and processes were implemented to reduce the potential for bias in study conduct and analysis. Regarding the data transfer from Parexel to Cytel, Parexel defined two distinct procedures: one for the blinded and another for the unblinded database transfer. As defined by specific Data Transfer Agreements, detailing who would receive data and what content was provided. Files were transferred to approved recipients via Parexel Secure File Transfer Protocol (sFTP) system. The dedicated team in Cytel reviewed data transfers from Parexel to confirm unblinded data. The first unblinded database was received by Cytel on 11 October 2021 after the 08 October 2021 interim database lock. Table 23 reports the list of attachments that demonstrates the above-described process.

Table 23: Documents regarding blinding of datasets and Cytel team members- Annex B

Document date	Document name
15-June-2021	Data Transfer Agreement - Blinded
01-October-2021	RAD1901-308 Blinding Checklist
30-September-2021	Data Transfer Agreement Unblinded
08-November-2022	Cytel Project Team List

- **Statistical methods**

The study was of superiority design. Analyses of the primary endpoints were performed based on assessments by the blinded IRC. Analyses based on investigator assessment were also performed as supportive analyses. Efficacy data were reviewed at prespecified intervals by an Independent Data Monitoring Committee (IDMC), as per the IDMC charter. An interim analysis for futility was performed by the IDMC at the time when approximately 70% enrolment had been achieved. The IDMC's recommendation was to continue the study unmodified.

The final PFS analysis was planned to be performed when approximately 160 PFS events (objective disease progression assessed by the blinded IRC or death) among the *ESR1*-mut subjects and 340 PFS events among all subjects (*ESR1*-mut + *ESR1*-mut-nd) had occurred. OS analyses were planned to be conducted at the same time as the final PFS analysis, and again when approximately 50% of subjects have died at which time the study will be considered complete.

Analysis populations for efficacy

Intention-to-Treat (ITT) Population: The ITT population included all randomized subjects. This was the primary population for PFS and OS analyses. Subjects were analysed according to their randomized treatment assignment.

Per-Protocol (PP) Population: The PP population included all randomized subjects who did not have any major protocol deviations that may confound the interpretation of the primary analyses conducted on the ITT population. The PP population was used to perform sensitivity analyses for the primary efficacy endpoint of PFS if the primary endpoint was statistically significant. Subjects were analysed according to their randomized treatment assignment.

Response-Evaluable (RE) Population: The RE population included all ITT subjects who had measurable disease (i.e., at least 1 target lesion) at baseline and at least 1 postbaseline RECIST assessment on any (target or nontarget) lesions and/or had a new lesion.

Clinical-Benefit-Evaluable (CBE) Population: The CBE population included all ITT subjects who had measurable and/or evaluable disease (i.e., target and/or nontarget lesions) at baseline and at least 1 postbaseline RECIST assessment on any (target or nontarget) lesions and/or had a new lesion.

Analysis methods

The SAP was finalized before database lock and unblinding.

For continuous variables, descriptive statistics included the number of subjects, mean, standard deviation, median, first quartile (Q1), third quartile (Q3), minimum, and maximum. For categorical variables, descriptive statistics included the number of subjects, frequency counts, and percentages. The Kaplan-Meier (KM) method was used to estimate the survival distribution function of PFS. The following summaries by treatment group were provided: median PFS and 95% confidence interval (CI),

Q1 and Q3 and 95% CI, PFS rates and 95% CI at Months 3, 6, and 12 (and every 6 months thereafter until the end of follow-up or no more subjects are at risk).

Primary endpoints

PFS was defined as the duration (in months) from the date of randomisation to the earliest date of documented disease progression per RECIST v1.1 or death due to any cause.

For subjects without objective disease progression or death, PFS was censored on the date of the last adequate tumour assessment or, if no tumour assessment was performed after the baseline visit, at the date of randomisation. Detailed censoring rules are described in Table 24.

Table 24: Rules for censoring date of progression or censor for Imaging Review Committee-assessed progression-free survival

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

Abbreviations: PFS = progression free survival.
Note: If more than 1 situation applies, date of PFS and associated outcome would be determined by the earliest date and associated previous outcome.
a 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.
b 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.

The difference in the primary endpoints between the treatment groups was to be analysed using a logrank test stratified by the factors used to stratify the randomisation. The HR and its 95% CI were to be estimated using the stratified Cox proportional hazards regression model with the Efron method of handling ties, stratified by the factors used to stratify the randomisation. The CIs for the HRs were to be constructed using the profile likelihood method. KM methods were to be used to display the time-to-event graphs and estimate the median event times and their 95% CIs, Q1 and Q3 and their 95% CIs, and the rates at Months 3, 6, 12, and 18 and their 95% CIs. The CIs for the medians, quartiles, and rates were to be constructed using the method of Brookmeyer and Crowley (Brookmeyer and Crowley 1982) via linear transformation. The primary analyses included the randomisation strata as the stratification factors.

The following sensitivity analyses were to be performed:

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

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

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.

In addition, **Restricted Mean Survival Time Analysis** (RMST) was to be performed. 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. Tau was 29.17 both for ITT and *ESR1*-mut patients and 25.89 for *ESR1*-mut-nd patients.

Key secondary endpoints

Analyses of OS in all subjects and in *ESR1*-mut subjects were to be performed using the ITT population.

The KM method was to be used to estimate median survival times, which were to be displayed with the survival curve. The Cox regression model that includes treatment and the stratification factors was used to estimate the HR and its 95% CI. The difference between treatment groups was to be analysed using the stratified log-rank test.

A sensitivity analysis for OS was to 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.

RMST analysis was also to be provided for the key secondary endpoints in a similar manner as IRC-assessed PFS.

Other secondary endpoints

Analyses of IRC-assessed PFS and OS in *ESR1*-mut-nd subjects were to be performed using the ITT population for the *ESR1*-mut-nd subjects, in the same manner as the analyses of the primary and key secondary efficacy endpoints.

Local investigator-assessed PFS was to be analysed in the same manner as IRC-assessed PFS.

IRC-assessed ORR was to be summarized using the RE population (defined based on IRC assessment) for *ESR1*-mut subjects, *ESR1*-mut-nd subjects, and all subjects (*ESR1*-mut + *ESR1*-mut-nd). The ORR was to be summarized as a binomial response rate with 95% CIs based on the ClopperPearson method. Comparison between treatment groups was to be performed using the Cochran-Mantel-Haenszel test adjusting for randomisation stratification factors.

IRC-assessed DoR was to 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 + *ESR1*-mut-nd).

IRC-assessed CBR was to be summarized using the CBE population (based on IRC assessment) for *ESR1*-mut subjects, *ESR1*-mut-nd subjects, and all subjects (*ESR1*-mut + *ESR1*-mut-nd). The IRC-assessed CBR was to be analysed in the same manner as the analysis of ORR.

In addition, local investigator-assessed ORR CBR, and DoR were to be analysed in the same matter as the IRC-assessed endpoints.

Patient-reported outcomes

Analyses of the PROs were to be performed using the ITT population for *ESR1*-mut subjects and all subjects (*ESR1*-mut + *ESR1*-mut-nd). For each set of study subjects, the PRO endpoint values and changes from baseline by visit were to be summarized by treatment group.

Exploratory endpoints

Time to chemotherapy was to be summarized by treatment group descriptively for the subjects who received chemotherapy as first systemic therapy after treatment discontinuation.

The other exploratory objectives, including changes in ctDNA and exploration of the relationship between these findings and clinical response, were to be analysed.

Handling of dropouts or missing data

The handling of missing dates was only described in the SAP for AE events and start of post-treatment systemic anti-cancer therapy. Missing data in PFS and OS were to be handled by censoring. In ORR these were to fall in the NE= not evaluable category and for the PROs the handling of missing data was to be defined in the questionnaires themselves.

Multiple comparisons/Multiplicity

To ensure the family-wide error rate does not exceed 5%, multiplicity adjustments were to 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. The multiplicity correction between the two timepoints for OS were to be done using the Haybittle-Peto method.

During the study, the OS analysis plan was changed with the addition of the formal test at the time of the primary PFS analysis.

A parallel gatekeeping strategy based on the truncated Hochberg procedure (Dmitrienko et al, *Journal of Biopharmaceutical Statistics,* 2011) was to 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 chosen truncation fraction is 0.9, resulting in α_1=0.0475 and α_2= 0.025.

- If the larger p-value is <0.0475, statistical significance will be claimed for both PFS endpoints (both populations). A full 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 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 <0.025, statistical significance will be claimed only for the endpoint associated with the smaller p-value. A reduced 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.
- If the larger p-value is ≥0.0475 and the smaller p-value is ≥0.025, no statistical significance will be claimed for PFS. In this case, no alpha will be passed along to OS. No claim regarding OS will be made.

No statistical significance can be claimed for any endpoints other than the primary and key secondary endpoints.

Subgroup analyses

Subgroup analyses of IRC-assessed PFS, OS, ORR, DoR, and CBR were to be performed in the same manner as the analyses using the ITT population for all subjects (*ESR1*-mut + *ESR1*-mut-nd) and for *ESR1*-mut subjects only for the following stratification factors:

- 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 were to be performed in the same manner as the analyses using the ITT population for all subjects (*ESR1*-mut + *ESR1*-mut-nd) and for *ESR1*-mut subjects only by the following categories:

- Age (< 65 years vs ≥ 65 years)
- Age (< 75 years vs ≥ 75 years)
- Race (Caucasian vs Asian vs Other)
- Region (Europe, North America, Asia, Other)
- Baseline Eastern Cooperative Oncology Group (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)

Results

- **Participant flow**

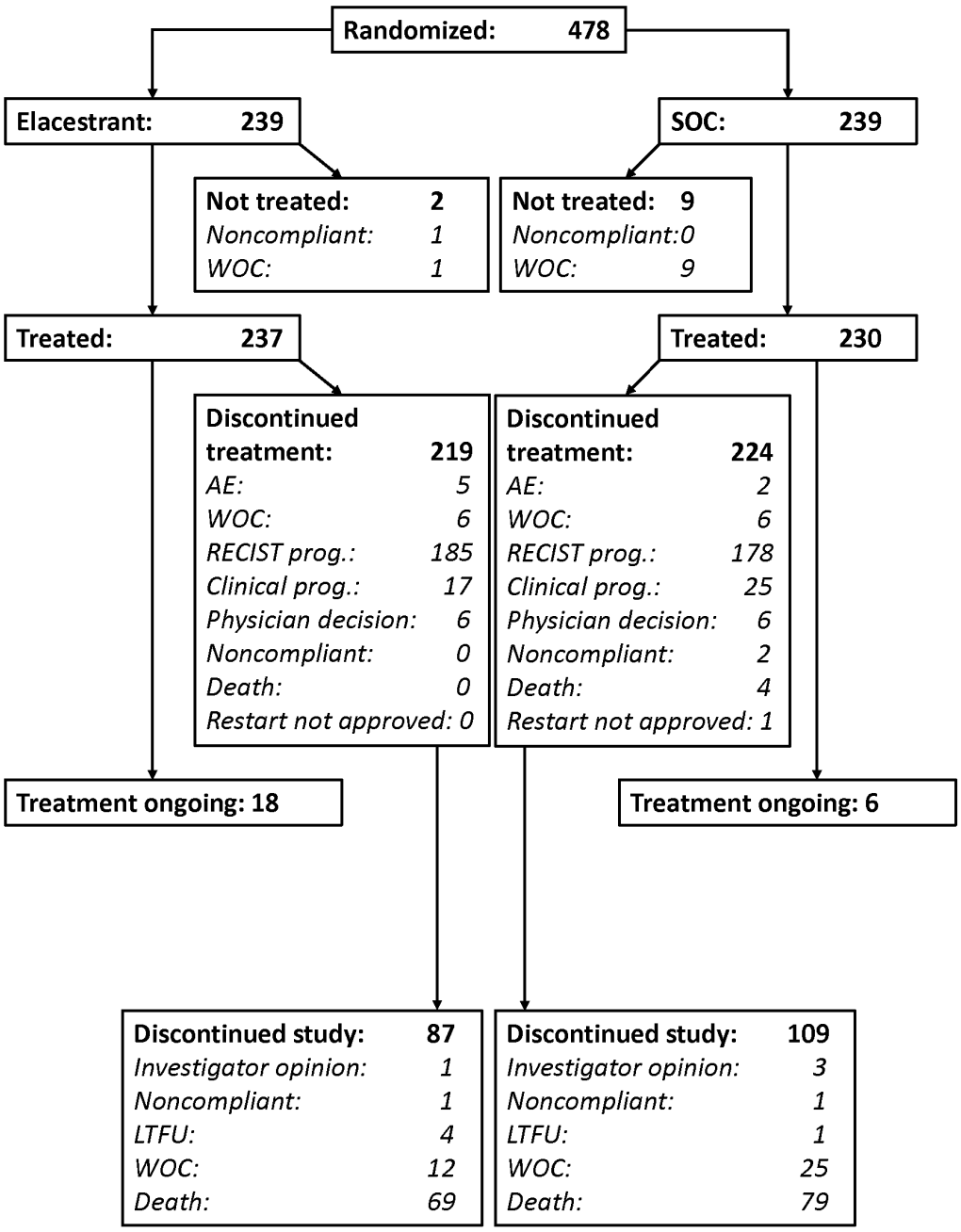
Overall, this study screened 695 subjects who granted informed consent for participation and randomized 478 subjects to treatment with either elacestrant or SOC. Of the 217 (31.2%) subjects who did not pass screening, 204 (29.4%) were excluded for failure to meet eligibility criteria, 10 (1.4%) due to withdrawal of consent, 2 (0.3%) due to the investigator's decision, and 1 (0.1%) due to significant noncompliance. Among the 204 patients who did not pass the screening for "failure to meet eligibility criteria", the most common reasons (>10% incidence) were inclusion criterion number 8 (prior treatment with 1-2 lines of endocrine therapy) in 30 (13.8%) patients and inclusion criterion number 13 (adequate organ function) in 39 (18.0%) patients. For 58 (26.7%) patients, a reason was not specified. The disposition of all subjects is shown in Figure 9.

Among all subjects, randomisation was equal to each group (239 elacestrant, 239 SOC). As of the DCO date (06 September 2021), 18 subjects (7.5%) in the elacestrant group and 6 subjects (2.5%) in the SOC group were still on treatment. Most subjects discontinued treatment (91.6% elacestrant, 93.7%

SOC). The most common reason for treatment discontinuation was investigator-assessed progression per RECIST criteria (77.4% elacestrant, 74.5% SOC).

Among *ESR1*-mut subjects, randomisation was equal to each group (115 elacestrant, 113 SOC). As of the DCO date (06 September 2021), 12 subjects (10.4%) in the elacestrant group and 3 subjects (2.7%) in the SOC group were still on treatment. Most subjects discontinued treatment (89.6% elacestrant, 91.2% SOC). The most common reason for treatment discontinuation was investigator-assessed progression per RECIST criteria (70.4% elacestrant, 77.9% SOC).

Figure 9: Subject Disposition (Study 308 - All Subjects)



Abbreviations: AE = adverse event; LTFU =lost to follow-up; prog. = progression; RECIST = Response Evaluation Criteria in Solid Tumours; SOC = standard of care; WOC = withdrawal of consent.
Source: Study 308, Table 14.1.1.1, Listing 16.2.1.1

In Table 25, the choice of SOC therapy per investigator is reported per prior therapy.

Table 25: Prior therapy in the metastatic setting and randomized treatment

	Randomized Treatment				
Prior treatment	**Elacestrant**	**Anastrozole**	**Exemestane**	**Fulvestrant**	**Letrozole**
Only AI	164 (68.6%)	0 (0.0%)	4 (7.3%)	154 (92.8%)	0 (0.0%)
Anastrozole	10 (4.2%)	0 (0.0%)	1 (1.8%)	16 (9.6%)	0 (0.0%)
Letrozole	154 (64.4%)	0 (0.0%)	4 (7.3%)	141 (84.9%)	0 (0.0%)
Exemestane	15 (6.3%)	0 (0.0%)	0 (0.0%)	12 (7.2%)	0 (0.0%)
Only Fulvestrant	39 (16.3%)	3 (42.9%)	27 (49.1%)	1 (0.6%)[a]	8 (72.7%)
AI and Fulvestrant	29 (12.1%)	4 (57.1%)	23 (41.8%)	5 (3.0%)	3 (27.3%)
Anastrozole	6 (2.5%)	0 (0.0%)	5 (9.1%)	1 (0.6%)	0 (0.0%)
Letrozole	21 (8.8%)	2 (28.6%)	20 (36.4%)	4 (2.4%)	1 (9.1%)
Exemestane	6 (2.5%)	2 (28.6%)	0 (0.0%)	1 (0.6%)	2 (18.2%)

Abbreviations: AI = aromatase inhibitor.
Only included patients with "Therapeutic" indicated as prior therapies setting
Percentages are calculated over the total number of patients for each study treatment in the ITT population.
Anastrozole: n = 7, Elacestrant: n = 239, Exemestane: n = 55, Fulvestrant: n = 166, Letrozole: n = 11.
a. One patient received prior fulvestrant plus abemaciclib combination for approximately 4 months before progression. Contrary to the protocol guidance, the investigator opted to assign the patient to fulvestrant in the control arm. The patient received the treatment at Cycle 1 Day 1 and at Cycle 1 Day 15 and then discontinued trial therapy because of disease progression also on Cycle 1 Day 15.
Data cut-off: 06 September 2021.
Source: EMERALD EMA Request, Table 7.1, Annex A.

- **Recruitment**

Subjects were enrolled in 17 countries at 150 of the 224 study sites initiated. The first patient was enrolled on 10 May 2019. The last patient last visit was not reached, as the study was ongoing as of the clinical data cut at 06 September 2021.

- **Conduct of the study**

Study amendments

All references in this report to the study protocol refer to version 6.0 unless otherwise stated.

Version 1.0 of the study protocol was dated 06 August 2018. Versions 2.0 through 4.0 of the protocol were issued in quick succession (see

Table 26). Version 4.0 (dated 22 August 2018) was the first protocol version under which subjects were recruited. The first patient was enrolled on 10 May 2019. After version 4.0, a further 2 global and several corresponding local protocol versions were issued. Versions 1.0 through 3.0 are not considered in the description in this report, as no subjects were treated under these versions. The main changes in the global amendments are discussed below.

Table 26: All protocol versions

Protocol Version	Date	Notes	N Subjects Recruited
1.0	06 August 2018	No recruitment	0
2.0	17 August 2018	No recruitment	0
3.0	22 August 2018	No recruitment	0
4.0	22 August 2018	Third global amendment	18
4.1	19 April 2019	Local amendment for the UK	0
4.2	25 April 2019	Local amendment for France	0
4.3		Canada	0
5.0	28 March 2019	Fourth global amendment	235
5.1	28 June 2019	Local amendment for the UK	6
5.2	10 July 2019	Local amendment for France	21
5.3		Local amendment for Canada	0
5.3.1	05 September 2019	Local amendment for Canada	3
6.0	25 March 2020	Fifth global amendment	175
6.0		France	14
6.0		Canada	1
6.1	26 March 2020	Local amendment for the UK	5

Abbreviations: N = number of subjects; UK = United Kingdom.
Source: Study 308, Table 14.1.1.3

Global changes from version 4.0 to version 5.0

The *ESR1*-WT population planned for some secondary analyses was changed to the *ESR1*-mut-nd population, the latter including subjects with no mutation detected as well as subjects with an unknown mutation status. Changes were made to study objectives and to the inclusion criteria reflecting this.

Prior fulvestrant treatment was only permitted > 42 days prior to the first dose of study drug, rather than > 28 days prior to the first dose of study drug as under version 4.0. Women with hormonally-induced menopause were excluded from the study. Subjects who discontinued a prior endocrine therapy due to toxicity without progression were excluded from the study. Subjects were required to have progressed during or within 28 days after completion of a line of prior combination therapy, including a CDK4/6i.

The inclusion criterion for cytotoxic chemotherapy was updated (see inclusion criterion 10).

Willingness to provide a tissue sample was removed as an inclusion criterion; this instead became an optional assessment, and an associated inclusion criterion was removed.

Renal function criteria were updated to include assessment by eGFR as an option alongside creatinine clearance. The requirement for male subjects to be on hormonal suppression was removed. Subjects with a Child-Pugh score of > 6 were excluded.

Response Evaluable and CBR Evaluable populations were added. An interim futility analysis at 70% enrolment was added.

Global changes from version 5.0 to version 6.0

This amendment provided clarification for inclusion and exclusion criteria, tumour and bone lesion assessments, prohibited medications (bisphosphonates and RANKL inhibitors except if on a stable dose), the Schedule of Events, provided details on the planned futility analysis, and expanded the list of inducers and inhibitors of CYP3A4/5 by adding moderate inhibitors and inducers.

Protocol deviations

Major protocol deviations were defined as a deviation from the basic requirements of the study protocol, including main inclusion and exclusion criteria; concomitant medication restrictions; dosing (i.e., outside of ± 20% prescribed dose of study drug); or any protocol requirements that resulted in a significant added risk to the study subject, had an impact on the quality of the data collected, or had an impact on the outcome of the study. This definition was included in the latest SAP version 1.1. The final classification of the deviations into major or minor was performed after database lock. Major protocol deviations are shown in Table 27 and were not included in the modified PP analysis. Most subjects had a minor deviation related to procedures/tests.

Table 27: Major protocol deviations (intent-to-treat population)

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

Abbreviations: Admin = administration; AE = adverse event; *ESR1* = estrogen receptor 1 gene; *ESR1*-mut = *ESR1* mutation; IP = investigational product; n = number of subjects with the observed group characteristic; N = total number of subjects in group; SOC = standard of care.
Source: Study 308, Table 14.1.19.2

In addition to the 17 patients with major protocol deviations, minor protocol deviations were reported in 472 (98.7%) patients. Of the 478 patients on study, 138 unique patients (71 elacestrant, 67 SOC) reported to have minor deviations involving either I/E criteria only (total 90 patients, elacestrant treated=48 patients and SOC treated=42 patients), ICFs only (total 37 patients, elacestrant=18 patients, SOC=19 patients) or both I/E criteria and ICF deviations (total 11, elacestrant=5 patients, SOC=6 patients).

Impact of the COVID-19 pandemic on study conduct and evaluation

The COVID-19 pandemic impacted the conduct of this study. Challenges led to issues such as quarantines, site closures and restrictions, travel limitations, and 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. Overall, 89 subjects had an average of 2.1 visits impacted. Almost all impacted visits (79 of 89 impacted visits) were either partially executed at site or by an alternative method. No subjects discontinued from the study due to the impact of COVID-19.

- **Baseline data**

Demographic and baseline characteristics

The median age of patients (elacestrant vs standard of care) at baseline was 63.0 years (range of 24-89) vs 63.5 (range of 32-83) and 45.0% were over 65 (43.5 vs 46.6). Among all subjects, there were 6 males (2.5%) in the elacestrant group and 1 male (0.4%) in the SOC group. All of the male subjects had *ESR1*-mut-nd status. All female subjects (N=471) were postmenopausal. All but 1 subject had an ECOG performance status of 0 or 1. The last subject had an ECOG = 1 at the time of screening and was considered eligible for randomisation. At the Cycle 1 Day 1 visit, the ECOG = 2.

Table 28: Baseline demographic characteristics (Study 308 - ITT population)

Demographic	All subjects				*ESR1*-mut subjects			
	Elacestrant N = 239		SOC N = 239		Elacestrant N = 115		SOC N = 113	
Age (years)								
Median (range)	63.0	(24-89)	63.0	(32-83)	64.0	(28-89)	63.0	(32-83)
Age group, n (%)								
< 65 years	135	(56.5)	128	(53.6)	62	(53.9)	62	(54.9)
≥ 65 years	104	(43.5)	111	(46.4)	53	(46.1)	51	(45.1)
≥ 75 years	40	(16.7)	46	(19.2)	17	(14.8)	17	(15.0)
Race, n (%)[a]								
n (missing)	190	(49)	195	(44)	94	(21)	92	(21)
Asian	16	(8.4)	16	(8.2)	5	(5.3)	8	(8.7)
Black or African American	5	(2.6)	8	(4.1)	4	(4.3)	4	(4.3)
White/Caucasian	168	(88.4)	170	(87.2)	84	(89.4)	80	(87.0)
Other	1	(0.5)	1	(0.5)	1	(1.1)	0	(0.0)
Gender, n (%)								
Male	6	(2.5)	1	(0.4)	0	(0.0)	0	(0.0)
Female	233	(97.5)	238	(99.6)	115	(100.0)	113	(100.0)
BMI (kg/m^2)								
n (missing)	236	(3)	237	(2)	113	(2)	112	(1)
Mean (SD)	27.58	(5.494)	27.92	(5.853)	28.07	(6.058)	27.88	(6.012)
ECOG performance status, n (%)								
0	143	(59.8)	135	(56.5)	67	(58.3)	62	(54.9)
1	96	(40.2)	103	(43.1)	48	(41.7)	51	(45.1)
> 1	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)

Abbreviations: BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; *ESR1* = oestrogen receptor 1 gene; *ESR1*-mut = *ESR1* mutation positive; ITT = intent-to-treat; n = number of subjects with the observed group characteristic; N = total number of subjects in group; SD = standard deviation; SOC = standard of care.

[a] Subjects could select more than one race.

Source: Study 308, Table 14.1.4.1

Table 29: Baseline demographic and disease characteristics – all patients (ITT population)

Characteristic		Elacestrant (N = 239)	Total SOC (N = 239)	Fulvestrant (N = 166)	AIs (N = 73)	Overall (N = 478)
Region	Total	239	239	166	73	478
	Asia	23 (9.6%)	27 (11.3%)	23 (13.9%)	4 (5.5%)	50 (10.5%)
	Europe	137 (57.3%)	121 (50.6%)	84 (50.6%)	37 (50.7%)	258 (54%)
	North America	65 (27.2%)	76 (31.8%)	48 (28.9%)	28 (38.4%)	141 (29.5%)
	Other	14 (5.9%)	15 (6.3%)	11 (6.6%)	4 (5.5%)	29 (6.1%)
Country	Total	239	239	166	73	478
	Argentina	8 (3.3%)	10 (4.2%)	6 (3.6%)	4 (5.5%)	18 (3.8%)
	Australia	6 (2.5%)	5 (2.1%)	5 (3%)	0 (0%)	11 (2.3%)
	Austria	2 (0.8%)	5 (2.1%)	5 (3%)	0 (0%)	7 (1.5%)
	Belgium	37 (15.5%)	33 (13.8%)	27 (16.3%)	6 (8.2%)	70 (14.6%)
	Canada	2 (0.8%)	3 (1.3%)	3 (1.8%)	0 (0%)	5 (1%)
	Denmark	4 (1.7%)	5 (2.1%)	2 (1.2%)	3 (4.1%)	9 (1.9%)
	France	18 (7.5%)	20 (8.4%)	18 (10.8%)	2 (2.7%)	38 (7.9%)
	Greece	3 (1.3%)	7 (2.9%)	2 (1.2%)	5 (6.8%)	10 (2.1%)
	Hungary	17 (7.1%)	12 (5%)	6 (3.6%)	6 (8.2%)	29 (6.1%)
	Ireland	4 (1.7%)	3 (1.3%)	0 (0%)	3 (4.1%)	7 (1.5%)
	Israel	9 (3.8%)	12 (5%)	9 (5.4%)	3 (4.1%)	21 (4.4%)
	Italy	19 (7.9%)	16 (6.7%)	9 (5.4%)	7 (9.6%)	35 (7.3%)
	Portugal	8 (3.3%)	4 (1.7%)	4 (2.4%)	0 (0%)	12 (2.5%)
	Republic of Korea	14 (5.9%)	15 (6.3%)	14 (8.4%)	1 (1.4%)	29 (6.1%)
	Spain	17 (7.1%)	12 (5%)	7 (4.2%)	5 (6.8%)	29 (6.1%)
	United Kingdom of Great Britain and Northern Ireland	8 (3.3%)	4 (1.7%)	4 (2.4%)	0 (0%)	12 (2.5%)
	United States of America	63 (26.4%)	73 (30.5%)	45 (27.1%)	28 (38.4%)	136 (28.5%)
Stage at Initial Diagnosis	Total	239	239	166	73	478
	Missing	0 (0%)	1 (0.4%)	1 (0.6%)	0 (0%)	1 (0.2%)
	I	35 (14.6%)	29 (12.1%)	20 (12%)	9 (12.3%)	64 (13.4%)
	II	80 (33.5%)	81 (33.9%)	54 (32.5%)	27 (37%)	161 (33.7%)
	III	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)
	IIIA	19 (7.9%)	20 (8.4%)	12 (7.2%)	8 (11%)	39 (8.2%)
	IIIB	7 (2.9%)	3 (1.3%)	2 (1.2%)	1 (1.4%)	10 (2.1%)
	IIIC	11 (4.6%)	7 (2.9%)	5 (3%)	2 (2.7%)	18 (3.8%)
	IIIUnknown	12 (5%)	11 (4.6%)	8 (4.8%)	3 (4.1%)	23 (4.8%)
	IV	62 (25.9%)	76 (31.8%)	59 (35.5%)	17 (23.3%)	138 (28.9%)
	IVUnknown	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)
	Unknown	11 (4.6%)	11 (4.6%)	5 (3%)	6 (8.2%)	22 (4.6%)
Prior Treatment with Fulvestrant	Total	239	239	166	73	478
	N	169 (70.7%)	164 (68.6%)	160 (96.4%)	4 (5.5%)	333 (69.7%)
	Y	70 (29.3%)	75 (31.4%)	6 (3.6%)	69 (94.5%)	145 (30.3%)
Presence of Visceral Metastases	Total	239	239	166	73	478
	N	81 (33.9%)	75 (31.4%)	53 (31.9%)	22 (30.1%)	156 (32.6%)
	Y	158 (66.1%)	164 (68.6%)	113 (68.1%)	51 (69.9%)	322 (67.4%)
ESR1 Mutation	Total	239	239	166	73	478

Characteristic		Elacestrant (N = 239)	Total SOC (N = 239)	Fulvestrant (N = 166)	AIs (N = 73)	Overall (N = 478)
	ESR1-mut	115 (48.1%)	113 (47.3%)	83 (50%)	30 (41.1%)	228 (47.7%)
	ESR1-mut-nd	124 (51.9%)	126 (52.7%)	83 (50%)	43 (58.9%)	250 (52.3%)
Child Pugh Class	Total	239	239	166	73	478
	Missing	2 (0.8%)	10 (4.2%)	4 (2.4%)	6 (8.2%)	12 (2.5%)
	Normal	203 (84.9%)	173 (72.4%)	124 (74.7%)	49 (67.1%)	376 (78.7%)
	Class A (mild)	33 (13.8%)	53 (22.2%)	37 (22.3%)	16 (21.9%)	86 (18%)
	Class B (moderate)	1 (0.4%)	3 (1.3%)	1 (0.6%)	2 (2.7%)	4 (0.8%)
NCI Classification (NCIc)	Total	239	239	166	73	478
	Missing	1 (0.4%)	9 (3.8%)	4 (2.4%)	5 (6.8%)	10 (2.1%)
	Normal	160 (66.9%)	146 (61.1%)	100 (60.2%)	46 (63%)	306 (64%)
	Mild Dysfunction-Group 1	77 (32.2%)	82 (34.3%)	61 (36.7%)	21 (28.8%)	159 (33.3%)
	Mild Dysfunction-Group 2	0 (0%)	2 (0.8%)	1 (0.6%)	1 (1.4%)	2 (0.4%)
	Moderate Dysfunction	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)
Renal impairment (GFR mL/min)*	Total	239	239	166	73	478
	< 15 (End stage renal disease ESRD - Requiring Dialysis Treatment)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	< 30 (Severely decreased renal function - Not Requiring Dialysis)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)
	30- < 60 (Moderately decreased renal function)	46 (19.2%)	44 (18.4%)	28 (16.9%)	16 (21.9%)	90 (18.8%)
	60- < 90 (Mildly decreased renal function)	86 (36%)	91 (38.1%)	62 (37.3%)	29 (39.7%)	177 (37%)

Characteristic		Elacestrant (N = 239)	Total SOC (N = 239)	Fulvestrant (N = 166)	AIs (N = 73)	Overall (N = 478)

Abbreviations: SOC = Standard of Care; AI = Aromatase Inhibitor; ESR1-mut = ESR1 mutation, ESR1-mut-nd = No ESR1 mutation detected; GFR = absolute Glomerular Filtration Rate; ITT = intent-to-treat; NCIc = National Cancer Institute classification.
* Based on EMA Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function (EMA/CHMP/83874/2014, 2015)
Child-Pugh and National Cancer Institute classifications for hepatic dysfunction.
Data cut-off: 08 July 2022.
Source: EMERALD EMA Request, Table 6.1, Annex A.

Table 30: Baseline demographic and disease characteristics – ESR1-mut patients (ITT population)

Characteristic		Elacestrant (N = 115)	Total SOC (N = 113)	Fulvestrant (N = 83)	AIs (N = 30)	Overall (N = 228)
Region	Total	115	113	83	30	228
	Asia	10 (8.7%)	16 (14.2%)	13 (15.7%)	3 (10%)	26 (11.4%)
	Europe	63 (54.8%)	50 (44.2%)	36 (43.4%)	14 (46.7%)	113 (49.6%)
	North America	33 (28.7%)	42 (37.2%)	30 (36.1%)	12 (40%)	75 (32.9%)
	Other	9 (7.8%)	5 (4.4%)	4 (4.8%)	1 (3.3%)	14 (6.1%)
Country	Total	115	113	83	30	228
	Argentina	6 (5.2%)	4 (3.5%)	3 (3.6%)	1 (3.3%)	10 (4.4%)
	Australia	3 (2.6%)	1 (0.9%)	1 (1.2%)	0 (0%)	4 (1.8%)
	Austria	2 (1.7%)	3 (2.7%)	3 (3.6%)	0 (0%)	5 (2.2%)
	Belgium	13 (11.3%)	12 (10.6%)	10 (12%)	2 (6.7%)	25 (11%)
	Canada	0 (0%)	2 (1.8%)	2 (2.4%)	0 (0%)	2 (0.9%)
	Denmark	1 (0.9%)	3 (2.7%)	2 (2.4%)	1 (3.3%)	4 (1.8%)
	France	9 (7.8%)	8 (7.1%)	8 (9.6%)	0 (0%)	17 (7.5%)
	Greece	0 (0%)	2 (1.8%)	0 (0%)	2 (6.7%)	2 (0.9%)
	Hungary	10 (8.7%)	4 (3.5%)	2 (2.4%)	2 (6.7%)	14 (6.1%)
	Ireland	2 (1.7%)	3 (2.7%)	0 (0%)	3 (10%)	5 (2.2%)
	Israel	6 (5.2%)	8 (7.1%)	5 (6%)	3 (10%)	14 (6.1%)
	Italy	8 (7%)	4 (3.5%)	1 (1.2%)	3 (10%)	12 (5.3%)
	Portugal	4 (3.5%)	3 (2.7%)	3 (3.6%)	0 (0%)	7 (3.1%)
	Republic of Korea	4 (3.5%)	8 (7.1%)	8 (9.6%)	0 (0%)	12 (5.3%)
	Spain	8 (7%)	5 (4.4%)	4 (4.8%)	1 (3.3%)	13 (5.7%)
	United Kingdom of Great Britain and Northern Ireland	6 (5.2%)	3 (2.7%)	3 (3.6%)	0 (0%)	9 (3.9%)
	United States of America	33 (28.7%)	40 (35.4%)	28 (33.7%)	12 (40%)	73 (32%)
Stage at Initial Diagnosis	Total	115	113	83	30	228
	Missing	0 (0%)	1 (0.9%)	1 (1.2%)	0 (0%)	1 (0.4%)
	I	15 (13%)	11 (9.7%)	9 (10.8%)	2 (6.7%)	26 (11.4%)
	II	27 (23.5%)	39 (34.5%)	27 (32.5%)	12 (40%)	66 (28.9%)
	III	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
	IIIA	5 (4.3%)	6 (5.3%)	3 (3.6%)	3 (10%)	11 (4.8%)
	IIIB	4 (3.5%)	0 (0%)	0 (0%)	0 (0%)	4 (1.8%)
	IIIC	4 (3.5%)	6 (5.3%)	4 (4.8%)	2 (6.7%)	10 (4.4%)
	IIIUnknown	7 (6.1%)	7 (6.2%)	6 (7.2%)	1 (3.3%)	14 (6.1%)
	IV	42 (36.5%)	38 (33.6%)	31 (37.3%)	7 (23.3%)	80 (35.1%)
	Unknown	10 (8.7%)	5 (4.4%)	2 (2.4%)	3 (10%)	15 (6.6%)
Prior Treatment with Fulvestrant	Total	115	113	83	30	228
	N	88 (76.5%)	85 (75.2%)	82 (98.8%)	3 (10%)	173 (75.9%)
	Y	27 (23.5%)	28 (24.8%)	1 (1.2%)	27 (90%)	55 (24.1%)
Presence of Visceral Metastases	Total	115	113	83	30	228
	N	36 (31.3%)	33 (29.2%)	25 (30.1%)	8 (26.7%)	69 (30.3%)
	Y	79 (68.7%)	80 (70.8%)	58 (69.9%)	22 (73.3%)	159 (69.7%)
Child Pugh Class	Total	115	113	83	30	228
	Missing	1 (0.9%)	7 (6.2%)	4 (4.8%)	3 (10%)	8 (3.5%)
	Normal	95 (82.6%)	71 (62.8%)	57 (68.7%)	14 (46.7%)	166 (72.8%)
	Class A (mild)	18 (15.7%)	32 (28.3%)	21 (25.3%)	11 (36.7%)	50 (21.9%)
	Class B (moderate)	1 (0.9%)	3 (2.7%)	1 (1.2%)	2 (6.7%)	4 (1.8%)
NCI Classification (NCIc)	Total	115	113	83	30	228
	Missing	0 (0%)	7 (6.2%)	4 (4.8%)	3 (10%)	7 (3.1%)
	Normal	71 (61.7%)	66 (58.4%)	48 (57.8%)	18 (60%)	137 (60.1%)
	Mild Dysfunction- Group 1	43 (37.4%)	39 (34.5%)	31 (37.3%)	8 (26.7%)	82 (36%)
	Mild Dysfunction- Group 2	0 (0%)	1 (0.9%)	0 (0%)	1 (3.3%)	1 (0.4%)
	Moderate Dysfunction	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
Renal impairment (GFR mL/min)*	Total	115	113	83	30	228
	< 15 (End stage renal disease ESRD - Requiring Dialysis Treatment)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	< 30 (Severely decreased renal function - Not Requiring Dialysis)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	30- < 60 (Moderately decreased renal function)	24 (20.9%)	20 (17.7%)	13 (15.7%)	7 (23.3%)	44 (19.3%)
	60- < 90 (Mildly decreased renal function)	45 (39.1%)	44 (38.9%)	31 (37.3%)	13 (43.3%)	89 (39%)

Abbreviations: SOC = Standard of Care; AI = Aromatase Inhibitor; ESR1-mut = ESR1 mutation, ESR1-mut-nd = No ESR1 mutation detected; GFR = absolute Glomerular Filtration Rate; ITT = intent-to-treat; NCIc = National Cancer Institute classification.
Child-Pugh and National Cancer Institute classifications for hepatic dysfunction.
Data cut-off: 08 July 2022.
Source: EMERALD EMA Request, Table 6.2, Annex A.

Baseline disease characteristics are shown in Table 29 and Table 31. The median time since initial diagnosis in all groups was between 4.92 and 6.28 years. Most subjects (65.3%) had ductal tumour histology. Metastatic sites were most commonly in the bone (78.9% [bone only: 14.0%]), liver (49.6%), lymph nodes (28.5%), and lung (26.23). Brain metastases were uncommon and was reported in 7 patients in total (1.5%).

In the *ESR1*-mut group, 1 subject did not have an *ESR1*-mut as per local assessment but was mis-stratified. The central laboratory later identified 2 additional subjects as having no *ESR1*-mut. All other subjects had at least 1 *ESR1*-mut.

There were two patients reported without ER-positive disease (1 in each treatment arm), see Table 31. One patient had missing ER status, however, per a query in the eCRF, the site later confirmed that this patient was considered ER+ based on Allred score that resulted in 8/8 and met inclusion criteria. For the other patient no pathology report was available for ER, PR, or HER2 per the eCRF. Per data queries the investigator reported the patient was ER+ due to prior tamoxifen use. Of note, all randomized patients at baseline, had at least 1 lesion (target or non-target) outside the breast, that is, metastatic, which indicates that the M status for all randomized patients at baseline was M1.

Table 31: Baseline disease characteristics (Study 308 - ITT population)

Baseline disease characteristic	**All subjects**				***ESR1*-mut subjects**			
	Elacestrant N = 239		**SOC N = 239**		**Elacestrant N = 115**		**SOC N = 113**	
Years since initial diagnosis								
Median (range)	6.28	(0.2-32.2)	6.11	(0.5-40.1)	4.92	(0.2-28.4)	5.75	(0.9-31.0)
Stage at baseline, n (%)								
IIA	1	(0.4)	1	(0.4)	1	(0.9)	0	(0.0)
IIIA	2	(0.8)	0	(0.0)	0	(0.0)	0	(0.0)
IIIC	1	(0.4)	1	(0.4)	0	(0.0)	1	(0.9)
IV	12	(5.0)	18	(7.5)	8	(7.0)	7	(6.2)
IVA	3	(1.3)	3	(1.3)	1	(0.9)	2	(1.8)
IVB	3	(1.3)	3	(1.3)	1	(0.9)	1	(0.9)
IVC	1	(0.4)	1	(0.4)	0	(0.0)	1	(0.9)
Unknown	194	(81.2)	192	(80.3)	91	(79.1)	88	(77.9)
T Stage at baseline, n (%)								
T1	8	(3.3)	5	(2.1)	2	(1.7)	2	(1.8)
T2	13	(5.4)	15	(6.3)	6	(5.2)	8	(7.1)
T3	6	(2.5)	4	(1.7)	3	(2.6)	0	(0.0)
T4	12	(5.0)	11	(4.6)	8	(7.0)	4	(3.5)
Unknown	54	(22.6)	54	(22.6)	24	(20.9)	25	(22.1)
N Stage at baseline, n (%)								
N0	14	(5.9)	12	(5.0)	8	(7.0)	3	(2.7)
N1	14	(5.9)	13	(5.4)	4	(3.5)	6	(5.3)
N2	7	(2.9)	7	(2.9)	4	(3.5)	3	(2.7)
N3	6	(2.5)	5	(2.1)	3	(2.6)	1	(0.9)
Unknown	52	(21.8)	54	(22.6)	24	(20.9)	27	(23.9)
M Stage at baseline, n (%)								
M0	8	(3.3)	6	(2.5)	3	(2.6)	0	(0.0)
M1	60	(25.1)	62	(25.9)	27	(23.5)	25	(22.1)

Baseline disease characteristic	All subjects				*ESR1*-mut subjects			
	Elacestrant N = 239		SOC N = 239		Elacestrant N = 115		SOC N = 113	
Unknown	26	(10.9)	24	(10.0)	13	(11.3)	14	(12.4)
Missing	145	(60.7%)	147	(61.5%)	72	(62.6%)	74	(65.5%)
Number of metastatic sites, n (%)								
1	51	(21.3)	46	(19.2)	16	(13.9)	19	(16.8)
2	74	(31.0)	72	(30.1)	43	(37.4)	34	(30.1)
≥ 3	78	(32.6)	83	(34.7)	44	(38.3)	41	(36.3)
Missing*	36	(15.1%)	38	(15.9%)	12	(10.4%)	19	(16.8%)
Histology, n (%)								
Ductal	154	(64.4)	158	(66.1)	74	(64.3)	77	(68.1)
Lobular	36	(15.1)	32	(13.4)	17	(14.8)	12	(10.6)
Other	20	(8.4)	15	(6.3)	10	(8.7)	6	(5.3)
Unknown	26	(10.9)	32	(13.4)	13	(11.3)	17	(15.0)
Histopathology grade, n (%)								
Grade 1	17	(7.1)	23	(9.6)	5	(4.3)	10	(8.8)
Grade 2	127	(53.1)	129	(54.0)	61	(53.0)	66	(58.4)
Grade 3	62	(25.9)	52	(21.8)	32	(27.8)	22	(19.5)
Oestrogen receptor, n (%)								
Positive	238	(99.6)	238	(99.6)	114	(99.1)	112	(99.1)
Progesterone receptor, n (%)								
Positive	168	(70.3)	181	(75.7)	82	(71.3)	85	(75.2)

Abbreviations: *ESR1* = oestrogen receptor 1 gene; *ESR1*-mut = *ESR1* mutation positive; ITT = intent-to-treat; n = number of subjects with the observed group characteristic; N = total number of subjects in group; SOC = standard of care.
Source: Study 308, Table 14.1.7.1 and Table 14.1.8

* All randomized patients at baseline, had at least 1 lesion (target or non-target) outside the breast, that is, metastatic, which indicates that the M status for all randomized patients at baseline was M1.

Prior systemic anticancer therapies

Prior systemic anticancer therapy is shown in Table 32. Consistent with the inclusion criteria, all subjects had at most 1 line of chemotherapy for advanced/metastatic disease and either 1 or 2 lines of endocrine therapy in the advanced or metastatic setting.

For all subjects, in any setting, prior AI therapy was reported for 235 subjects in the elacestrant group and 231 subjects in the SOC group. The median duration of AI therapy was 25.0 months (range 2 to 164 months) in the elacestrant group and 24.3 months (2 to 154 months) in the SOC group. Similar proportions and durations of therapy were observed for *ESR1*-mut subjects. All subjects had prior CDK4/6i therapy in any setting.

Table 32: Prior systemic anticancer therapies (intent-to-treat population)

	n (%)							
	All Subjects				*ESR1*-mut Subjects			
	Elacestrant N = 239		SOC N = 239		Elacestrant N = 115		SOC N = 113	
Neoadjuvant/adjuvant setting								
Number of subjects with neoadjuvant therapy	38	(15.9)	37	(15.5)	17	(14.8)	14	(12.4)
Number of subjects with adjuvant therapy	158	(66.1)	142	(59.4)	62	(53.9)	65	(57.5)
Number of subjects with neo/adjuvant endocrine therapy								
Fulvestrant	4	(1.7)	1	(0.4)	1	(0.9)	–	–
AI	91	(38.1)	81	(33.9)	34	(29.6)	39	(34.5)
Tamoxifen	89	(37.2)	82	(34.3)	36	(31.3)	39	(34.5)
Number of subjects with neo/adjuvant targeted therapy	2	(0.8)	1	(0.4)	1	(0.9)	–	–
Advanced/metastatic setting								
Number of lines of endocrine therapy with documented progression in the adv/met setting								
1	129	(54.0)	142	(59.4)	73	(63.5)	69	(61.1)
2	110	(46.0)	97	(40.6)	42	(36.5)	44	(38.9)
Number of lines of chemotherapy for adv/met disease								
0	191	(79.9)	180	(75.3)	89	(77.4)	81	(71.7)
1	48	(20.1)	59	(24.7)	26	(22.6)	32	(28.3)
Number of lines of targeted therapy for adv/met disease								
1	–	–	4	(1.7)	–	–	1	(0.9)
2	9	(3.8)	4	(1.7)	6	(5.2)	1	(0.9)
> 2	1	(0.4)	1	(0.4)	–	–	1	(0.9)
Number of subjects with prior therapies for adv/met disease								
Any prior endocrine therapy	232	(97.1)	234	(97.9)	112	(97.4)	109	(96.5)
Any prior AI	193	(80.8)	194	(81.2)	101	(87.8)	96	(85.0)
Any prior tamoxifen	19	(7.9)	15	(6.3)	9	(7.8)	9	(8.0)
Any prior CDK4/6 inhibitor	239	(100.0)	239	(100.0)	115	(100.0)	113	(100.0)
Any prior fulvestrant	70	(29.3)	75	(31.4)	27	(23.5)	28	(24.8)
Any prior immunotherapy	3	(1.3)	–	–	1	(0.9)	–	–
Any other therapy	2	(0.8)	8	(3.3)	–	–	4	(3.5)
Time from last prior therapy to randomization (months)								
Mean (s.d.)	17.2	(12.7)	19.3	(13.51)	18.5	(12.52)	19.2	(13.21)

Abbreviations: Adv = advanced; AI = aromatase inhibitor; *ESR1* = estrogen receptor 1 gene; *ESR1*-mut = *ESR1* mutation; Met = metastatic; n = number of subjects with the observed group characteristic; N = total number of subjects in group; s.d. = standard deviation; SOC = standard of care.

Time from last prior therapy is from the start of the last prior therapy
Source: Study 308, Table 14.1.9.1

- **Numbers analysed**

Table 33: Data sets

	n (%)							
	All Subjects				*ESR1*-mut Subjects			
	Elacestrant		SOC		Elacestrant		SOC	
Population	N = 239		N = 239		N = 115		N = 113	
ITT	239	(100.0)	239	(100.0)	115	(100.0)	113	(100.0)
Modified Per-protocol	233	(97.5)	228	(95.4)	114	(99.1)	105	(92.9)
Safety	237	(99.2)	230	(96.2)	115	(100.0)	106	(93.8)
IRC-assessed RE	179	(74.9)	182	(76.2)	85	(73.9)	86	(76.1)
PI-assessed RE	189	(79.1)	192	(80.3)	91	(79.1)	92	(81.4)
IRC-assessed CBE	228	(95.4)	215	(90.0)	108	(93.9)	104	(92.0)
PI-assessed CBE	228	(95.4)	212	(88.7)	108	(93.9)	100	(88.5)

Abbreviations: CBE = clinical benefit evaluable; *ESR1* = estrogen receptor 1 gene; *ESR1* mut = *ESR1* mutation; IRC = Imaging Review Committee; ITT = intent-to-treat; n = number of subjects with the observed group characteristic; N = total number of subjects in group; PI = principal investigator; RE = response evaluable; SOC = standard of care.
Source: Study 308, Table 14.1.3

- **Outcomes and estimation**

In Study 308, both primary endpoints of PFS in all subjects and in *ESR1*-mut subjects were met.

Although the protocol specified that the final PFS analysis would be conducted when 160 events of objective disease progression (based on IRC assessment) or death had occurred among the *ESR1*-mut subjects and 340 events had occurred among all subjects, the final PFS analysis was actually conducted when there were 140 and 300 events, respectively (Table 34). The decision to modify the plan was based on a blinded PFS event projection analysis prior to database lock and unblinding.

To help plan the dates for database lock and the final PFS analysis, projections of the total numbers of IRC-assessed PFS events and their timing were estimated based on the total number of events that had accrued at the time of the projection analysis. These projections were calculated approximately monthly when data were transferred from Parexel the (Contract research organisation (CRO) in charge of running the study and also for Data Management activities to Cytel (contractor vendor for biostatistics activities). These projections were based on analyses using events pooled across the 2 treatment arms without regard to treatment.
The latest projection of IRC-assessed PFS events used the IRC PFS data transfer date of 19 July 2021. The analysis showed the median PFS of 3.70 in the all-patient population and 4.08 in the ESR1-mut population were each less than the median PFS of 5.3 used in the sample size calculations. The higher-than-expected rate of censoring and the number of patients still on treatment on 19 July 2021 indicated the protocol planned number of IRC-assessed PFS events (340) was unlikely to be achieved even in a year's time and a decision was therefore made to lock the database on 08 October 2021 based on a cut-off date of 06 September 2021.

The decision was made with the knowledge that PFS analyses, with approximately 300, instead of 340 events, would achieve 90% power to detect the pre-planned HR of 0.67 among all patients, and approximately 75% to 80% power to detect the pre-planned HR of 0.61 in the ESR1-mut patient population if the last patient was enrolled in late August 2021 and 07 October 2021 was the database lock date.

This study was ongoing as of the clinical data cutoff date of 06 September 2021. The results present the final analysis for the primary endpoints of PFS in all subjects and in only *ESR1*-mut subjects. Since OS data were not mature at the time of the interim analysis (data cutoff [DCO] date: 06 September 2021), additional post hoc analyses were conducted to explore the estimated probability of success at the time of the final OS analysis.

The final analysis of OS was made once 50% of subjects enrolled in the study have died (DCO: 02 September 2022).

Primary endpoint: Progression-free survival (blinded IRC assessment)

The analysis of the blinded IRC assessment of PFS is shown in Table 34 and landmark analysis in Table 35.

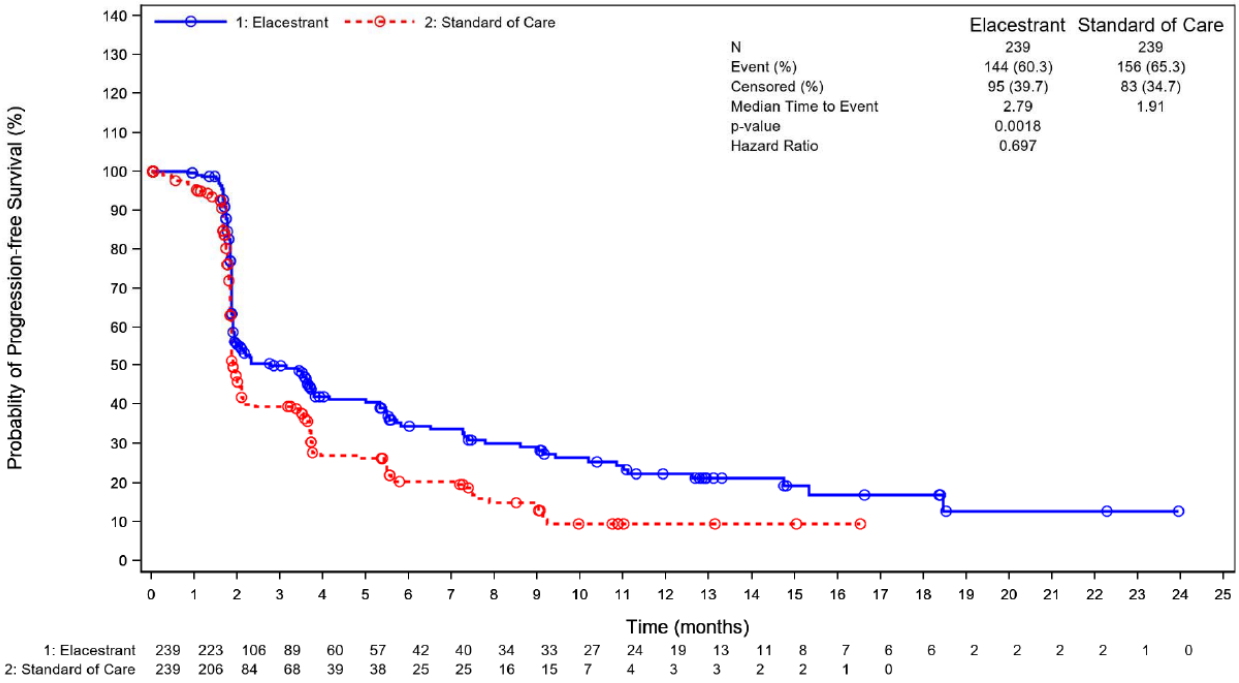
In all subjects, PFS was statistically significantly improved in subjects randomized to elacestrant compared to SOC (p = 0.0018, stratified log-rank test). The HR was 0.697 (95% CI: 0.5520-0.880), that is, a 30% reduction in the hazard of progression or death relative to the control arm. The median PFS was 2.79 months in the elacestrant group versus 1.91 months in the SOC group.

In *ESR1*-mut subjects, PFS was statistically significantly improved in subjects randomized to elacestrant compared to SOC (p = 0.0005, stratified log-rank test). The HR was 0.546 (95% CI: 0.387-0.768), that is, a 45% reduction in the hazard of progression or death relative to the control arm. The median PFS was 3.78 months in the elacestrant group versus 1.87 months in the SOC group.

The higher p-value was < 0.0475; thus, both primary objectives were met with statistical significance under the multiplicity correction methods used for this study.

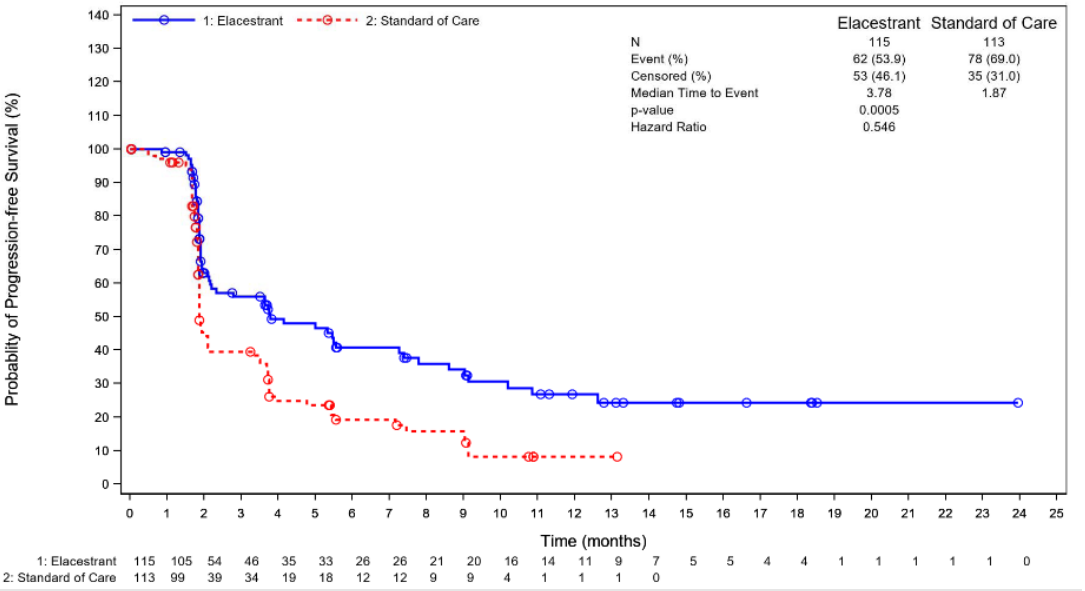
A KM plot of PFS is shown in Figure 10 (for all subjects) and in Figure 11 (for *ESR1*-mut subjects).

Figure 10: KM Plot for blinded IRC assessment of PFS in all subjects (Study 308 - ITT Population)



Abbreviations: CI = confidence interval; HR = hazard ratio; IRC = imaging review committee; ITT = intent-to-treat; KM = Kaplan-Meier; n = total number of subjects in group; No. = number; PFS = progression-free survival; SOC = standard of care.
Source: Study 308, Figure 14.2.1.1.2

Figure 11: KM plot for blinded IRC assessment of PFS in ESR1-mut subjects (Study 308 - ITT Population)



Abbreviations: CI = confidence interval; *ESR1* = oestrogen receptor 1 gene; *ESR1*-mut = *ESR1* mutation positive; HR = hazard ratio; IRC = imaging review committee; ITT = intent-to-treat; KM = Kaplan-Meier; n = total number of subjects in group; No. = number; PFS = progression-free survival; SOC = standard of care.
Source: Study 308, Figure 14.2.1.1.1

Table 34: Analysis of blinded IRC assessment of PFS (Study 308 - ITT Population)

	All subjects				*ESR1*-mut subjects			
	Elacestrant N = 239		SOC N = 239		Elacestrant N = 115		SOC N = 113	
HR (95% CI)[a]	0.697 (0.552-0.880)				0.546 (0.387-0.768)			
p-value[b]	0.0018				0.0005			
Median PFS (months)[c]	2.79		1.91		3.78		1.87	
95% CI[c]	1.94-3.78		1.87-2.10		2.17-7.26		1.87-2.14	
Events, n (%)	144	(60.3)	156	(65.3)	62	(53.9)	78	(69.0)
Death before progression	5	(2.1)	6	(2.5)	3	(2.6)	1	(0.9)
Progression	139	(58.2)	150	(62.8)	59	(51.3)	77	(68.1)
Censored, n (%)	95	(39.7)	83	(34.7)	53	(46.1)	35	(31.0)
No progression	69	(28.9)	46	(19.2)	39	(33.9)	19	(16.8)
Progression or death after ≥ 2 missed postbaseline assessments[d]	9	(3.8)	8	(3.3)	5	(4.3)	3	(2.7)
Progression or death after new anticancer therapy	6	(2.5)	9	(3.8)	3	(2.6)	4	(3.5)
No baseline measurable or evaluable lesion	1	(0.4)	1	(0.4)	0	(0.0)	0	(0.0)
Alive without postbaseline assessment	6	(2.5)	15	(6.3)	4	(3.5)	8	(7.1)
LTFU or WOC	4	(1.7)	4	(1.7)	2	(1.7)	1	(0.9)

Abbreviations: CI = confidence interval; *ESR1* = oestrogen receptor 1 gene; *ESR1*-mut = *ESR1* mutation positive; HR = hazard ratio; IRC = imaging review committee; ITT = intent-to-treat; KM = Kaplan-Meier; LTFU = loss to follow-up; n = number of subjects with the observed group characteristic; N = total number of subjects in group; PFS = progression-free survival; SOC = standard of care; WOC = withdrawal of consent.

[a] The analysis was performed using a stratified Cox proportional hazards model with ties=Efron and the stratification factors: prior treatment with fulvestrant (yes vs no) and presence of visceral metastases (yes vs no); the CI calculated using a profile likelihood method.

[b] The p-value was generated by using a 2-sided stratified log-rank test.

[c] Calculated using KM technique. CI for median PFS is derived based on the Brookmeyer-Crowley method using a linear transformation.

[d] Date of last tumour assessment before missed assessments or date of randomization, whichever is later.

Source: Study 308, Table 14.2.1.1.1 and Table 14.2.1.1.2

Table 35: Analysis of blinded IRC assessment of PFS rate (Study 308 – ITT Population)

Time point	PFS rate (%)[a] (95% CI)			
	All subjects		*ESR1*-mut subjects	
	Elacestrant N = 239	SOC N = 239	Elacestrant N = 115	SOC N = 113
3 months	49.75 (42.85-56.65)	39.29 (32.28-46.31)	55.93 (45.80-66.05)	39.55 (29.44-49.65)
6 months	34.32 (27.16-41.47)	20.38 (14.09-26.67)	40.76 (30.10-51.43)	19.14 (10.52-27.76)

Time point	PFS rate (%)[a] (95% CI)			
	All subjects		*ESR1*-mut subjects	
	Elacestrant N = 239	SOC N = 239	Elacestrant N = 115	SOC N = 113
12 months	22.32 (15.24-29.40)	9.42 (4.02-14.81)	26.76 (16.17-37.36)	8.19 (1.26-15.12)
18 months	16.82 (9.02-24.62)	—	24.33 (13.68-34.98)	—

Abbreviations: CI = confidence interval; *ESR1* = oestrogen receptor 1 gene; *ESR1*-mut = *ESR1* mutation positive; IRC = imaging review committee; ITT = intent-to-treat; KM = Kaplan-Meier; N = total number of subjects in group; PFS = progression-free survival; SOC = standard of care.

[a] Calculated using KM technique. CI for PFS is derived based on the Brookmeyer-Crowley method using a linear transformation.

Source: Study 308, Table 14.2.1.1.1 and Table 14.2.1.1.2

Key secondary endpoint: Overall survival

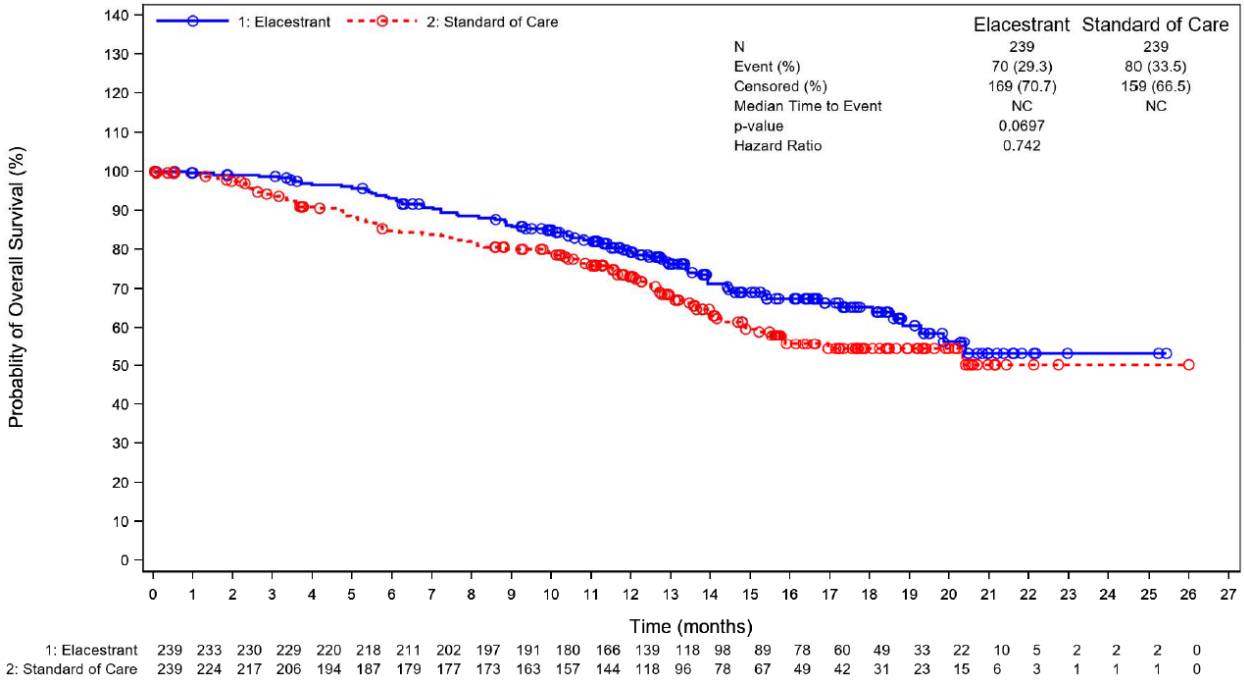
At the time of the DCO date (06 September 2021), an interim analysis for OS was performed. An updated final analysis was provided during the procedure with data cut-off date 02 September 2022. At the 06 September 2021 DCO, a total of 57 subjects were censored for overall survival due to withdrawal of consent, physician decision, or lost to follow-up. All sites were contacted. The vast majority of the sites refused to give updated survival information or were non-responsive.

The interim analysis used an alpha level of 0.0001 to control the overall Type I error rate of 5%. Results from this interim analysis of OS are shown in Table 36 and landmark analysis in Table 37.

- In all subjects, the HR for death was 0.742 (95% CI: 0.536-1.025). At an alpha level of 0.0001, the difference in OS between the elacestrant and SOC groups was not statistically significant (p = 0.0697, stratified log-rank test). A KM plot of OS for all subjects is shown in Figure 12.
- In *ESR1*-mut subjects, the HR for death was 0.592 (95% CI: 0.361-0.958). At an alpha level of 0.0001, the difference in OS between the elacestrant and SOC groups was not statistically significant (p = 0.0325, stratified log-rank test). A KM plot of OS for *ESR1*-mut subjects is shown in Figure 13.

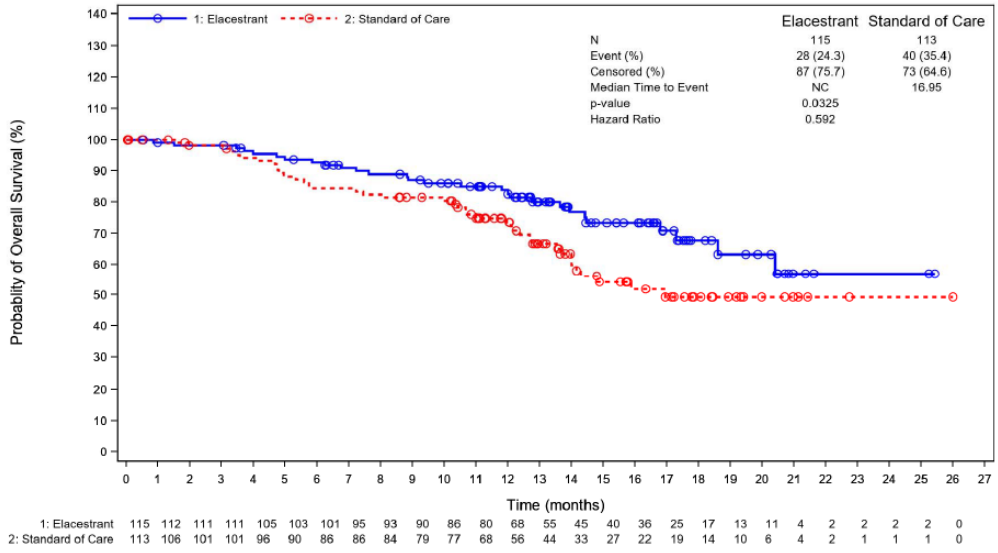
Among all subjects, 30 (12.6%) in the SOC group compared to 18 (7.5%) in the elacestrant group were censored due to withdrawal of consent. A majority of subjects in all groups were censored as still alive at DCO.

Figure 12: KM plot for OS in all subjects (Study 308 - ITT Population)



Abbreviations: ITT = intent-to-treat; KM = Kaplan-Meier; N = total number of subjects in group; NC = not calculable; OS = overall survival.
Source: Study 308, Figure 14.2.2.1.2

Figure 13: KM plot for OS in ESR1-mut subjects (Study 308 - ITT Population)



Abbreviations: *ESR1* = oestrogen receptor 1 gene; *ESR1*-mut = *ESR1* mutation positive; ITT = intent-to-treat; KM = Kaplan-Meier; N = total number of subjects in group; NC = not calculable; OS = overall survival.
Source: Study 308, Figure 14.2.2.1.1

Table 36: Analysis of OS (Study 308 - ITT Population)

	All subjects				*ESR1*-mut subjects			
	Elacestrant N = 239		SOC N = 239		Elacestrant N = 115		SOC N = 113	
HR (95% CI)[a]	0.742 (0.536-1.025)				0.592 (0.361-0.958)			
p-value[b]	0.0697				0.0325			
Median OS (months)[c]	NC		NC		NC		16.95	
95% CI[c]	19.29-NC		15.80-NC		18.60-NC		14.00-NC	
Death, n (%)	70	(29.3)	80	(33.5)	28	(24.3)	40	(35.4)
Censored, n (%)	169	(70.7)	159	(66.5)	87	(75.7)	73	(64.6)
Still alive[d]	144	(60.3)	125	(52.3)	72	(62.6)	60	(53.1)
Terminated prior to death[e]	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
LTFU	2	(0.8)	2	(0.8)	2	(1.7)	1	(0.9)
WOC	18	(7.5)	30	(12.6)	11	(9.6)	12	(10.6)
Other[f]	4	(1.7)	2	(0.8)	2	(1.7)	0	(0.0)

Abbreviations: CI = confidence interval; DCO = data cutoff; *ESR1* = oestrogen receptor 1 gene; *ESR1*-mut = *ESR1* mutation positive; HR = hazard ratio; ITT = intent-to-treat; KM = Kaplan-Meier; LTFU = loss to follow-up; n = number of subjects with the observed group characteristic; N = total number of subjects in group; NC = not calculable; OS = overall survival; SOC = standard of care; WOC = withdrawal of consent.

[a] The analysis was performed using a stratified Cox proportional hazards model with ties=Efron and the stratification factors: prior treatment with fulvestrant (yes vs no) and presence of visceral metastases (yes vs no); the CI calculated using a profile likelihood method.

[b] The p-value was generated by using a 2-sided stratified log-rank test.

[c] Calculated using KM technique. CI for median OS is derived based on the Brookmeyer-Crowley method using a linear transformation.

[d] Includes subjects known to be alive at DCO (06 September 2021).

[e] Includes subjects with unknown survival status.

[f] Includes any reason other than LTFU and WOC.

Source: Study 308, Table 14.2.2.1.1 and Table 14.2.2.1.2

Table 37: Analysis of OS rate (Study 308 – ITT Population)

Time point	OS rate (%)[a] (95% CI)			
	All subjects		*ESR1*-mut subjects	
	Elacestrant N = 239	SOC N = 239	Elacestrant N = 115	SOC N = 113
3 months	98.72 (97.28-100)	94.18 (91.11-97.25)	98.24 (95.82-100)	98.09 (95.46-100)
6 months	93.01 (89.71-96.32)	84.84 (80.07-89.61)	92.79 (87.97-97.60)	84.36 (77.32-91.40)
12 months	79.27 (73.84-84.71)	73.00 (66.90-79.11)	82.64 (75.28-90.00)	73.58 (64.80-82.37)
18 months	65.24 (57.85-72.64)	54.38 (46.18-62.57)	67.81 (56.22-79.40)	49.36 (37.03-61.70)

Abbreviations: CI = confidence interval; *ESR1* = oestrogen receptor 1 gene; *ESR1*-mut = *ESR1* mutation positive; ITT = intent-to-treat; KM = Kaplan-Meier; N = total number of subjects in group; OS = overall survival; SOC = standard of care.

[a] Calculated using KM technique. CI for OS is derived based on the Brookmeyer-Crowley method using a linear transformation.

Source: Study 308, Table 14.2.2.1.1 and Table 14.2.2.1.2

Final OS analysis

An updated analysis for overall survival was performed with a cut-off date of 02 September 2022 with a median follow-up for OS of 26.0 months for both the overall population as the ESR1 mut population. Summary results are presented in Table 38 below. The difference was not statistically significant. Study 308 is still ongoing and further follow up for survival is ongoing.

Table 38: Final analysis for overall survival (intent-to-treat population)

	All subjects		ESR1-mut subjects	
	Elacestrant (N = 239)	**SoC (N = 239)**	**Elacestrant (N = 115)**	**SoC (N = 113)**
HR (95% CI)[a]	0.912 (0.708-1.175)		0.903 (0.629-1.298)	
p-value[b]	0.48		0.58	
Median OS (months)[c]	24.61	22.57	24.18	23.49
95% CI[c]	20.67- 29.47	18.14-28.88	20.53-28.71	15.64-29.90
6 months	93.01	84.87	92.79	84.36
12 months	78.97	73.84	83.11	74.38
18 months	64.65	57.33	69.09	53.27
24 months	51.00	48.84	50.71	49.02

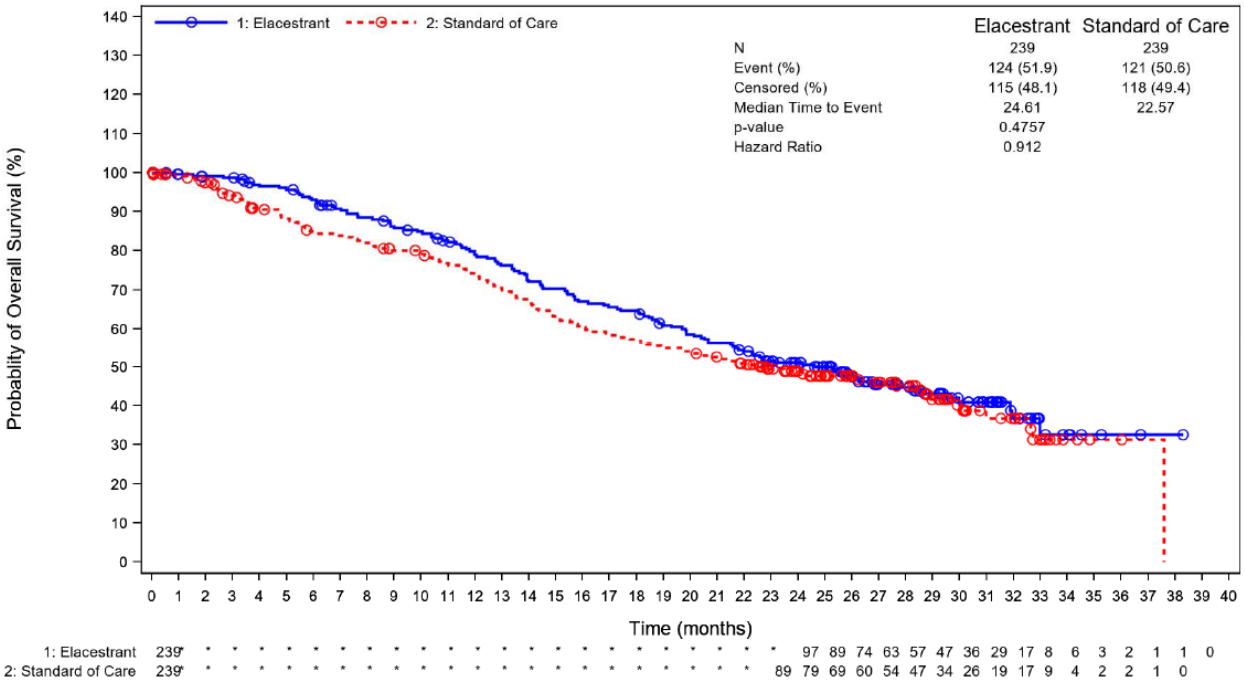
Abbreviations: CI = confidence interval; ESR1 = estrogen receptor 1 gene; ESR1-mut = ESR1 mutation positive; ESR1-mut-nd = ESR1 mutation not detected; HR = hazard ratio; IRC = Imaging Review Committee; KM = Kaplan-Meier; ITT = intent-to-treat; N = total number of subjects in group; OS = Overall survival; SoC = standard of care.

a. The analysis was performed using a stratified Cox proportional hazards model with ties = Efron and the stratification factors: prior treatment with fulvestrant (yes vs no) and presence of visceral metastases (yes vs no); the CI calculated using a profile likelihood method.
b. The p-value was generated by using a 2-sided stratified log-rank test.
c. Calculated using KM technique. CI for median is derived based on the Brookmeyer-Crowley method using a linear transformation.

Data cut-off date: 02 September 2022.
Source: EMERALD EMA Request, Table 22.4.1-.2, Annex A.

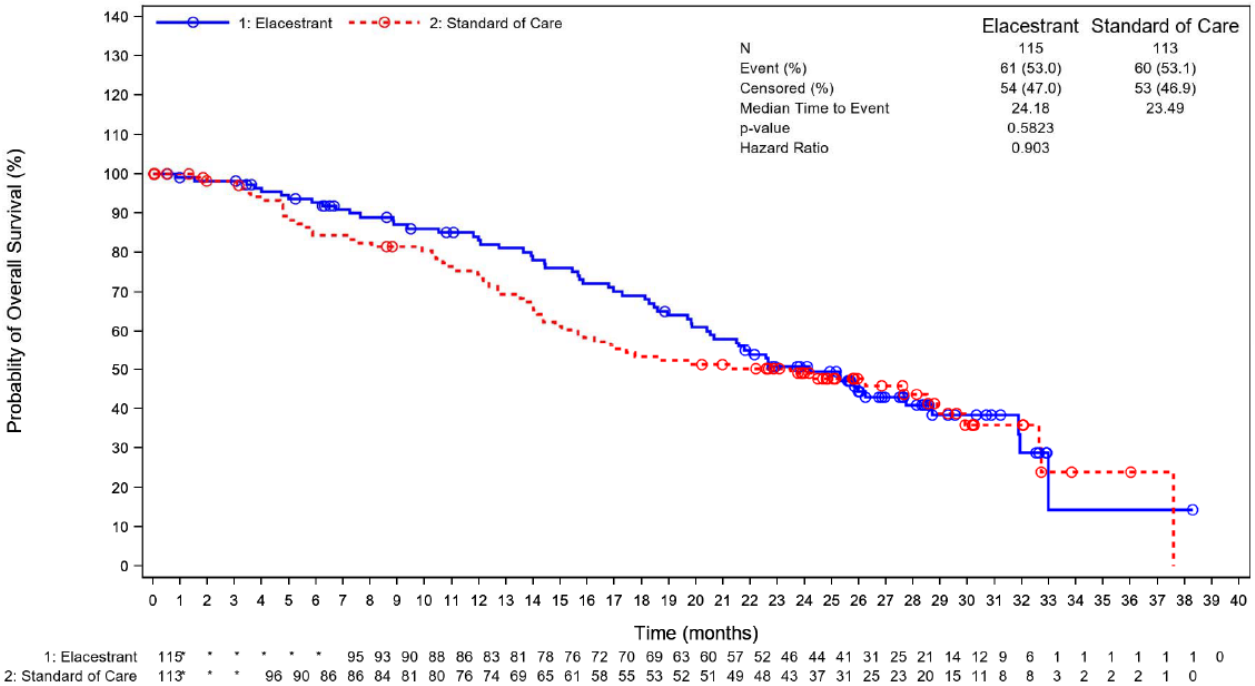
Kaplan-Meier curves for the OS analysis with cut-off date 02 September 2022 for all patients and ESR1-mut populations are provided in Figure 14 and Figure 15.

Figure 14: Kaplan-Meier plot of overall survival for elacestrant vs SOC, in all subjects at the time of final OS analysis (intent-to-treat population)



Database cut-off date: 02SEP2022, Database extraction date: 13OCT2022
Source: Emerald-308_OS_Figures 14.2.2.1.2

Figure 15: Kaplan-Meier plot of overall survival for elacestrant vs SOC, in ESR1-mut subjects at the time of final OS analysis (intent-to-treat population)



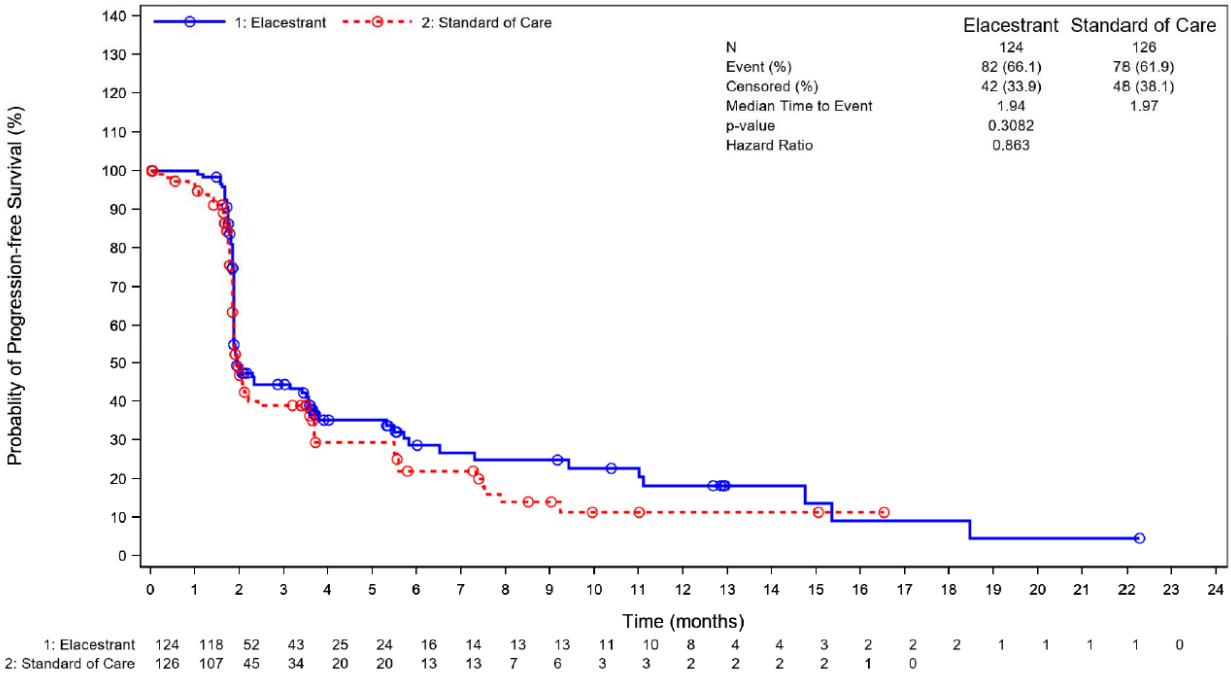
Database cut-off date: 02SEP2022, Database extraction date: 13OCT2022
Source: Emerald-308_OS_Figures 14.2.2.1.1

Other secondary endpoints

Progression-free survival in *ESR1*-mut-nd subjects (blinded IRC assessment)

The analysis of the blinded IRC assessment of PFS in *ESR1*-mut-nd subjects is shown in Table 39 and landmark analysis in Table 40. In *ESR1*-mut-nd subjects, HR for PFS was 0.863 (95% CI: 0.628-1.186), p = 0.3082, stratified log-rank test). A KM plot of PFS for *ESR1*-mut-nd subjects is shown in Figure 16.

Figure 16: KM plot for blinded IRC assessment of PFS in ESR1-mut-nd subjects (Study 308 - ITT population)



Abbreviations: *ESR1* = oestrogen receptor 1 gene; *ESR1*-mut-nd = no *ESR1* mutation detected; IRC = imaging review committee; ITT = intent-to-treat; KM = Kaplan-Meier; N = total number of subjects in group; PFS = progression-free survival.
Source: Study 308, Figure 14.2.1.1.3

Table 39: Analysis of blinded IRC assessment of PFS in ESR1-mut-nd Subjects (Study 308 - ITT Population)

	Elacestrant N = 124		SOC N = 126	
HR (95% CI)[a]	0.863 (0.628-1.186)			
p-value[b]	0.3082			
Median PFS (months)[c]	1.94		1.97	
95% CI[c]	1.87-3.55		1.87-2.20	
Events, n (%)	82	(66.1)	78	(61.9)
Death before progression	2	(1.6)	5	(4.0)
Progression	80	(64.5)	73	(57.9)
Censored, n (%)	42	(33.9)	48	(38.1)

	Elacestrant N = 124		SOC N = 126	
No progression	30	(24.2)	27	(21.4)
Progression or death after ≥ 2 missed postbaseline assessments[d]	4	(3.2)	5	(4.0)
Progression or death after new anticancer therapy	3	(2.4)	5	(4.0)
No baseline measurable or evaluable lesion	1	(0.8)	1	(0.8)
Alive without postbaseline assessment	2	(1.6)	7	(5.6)
LTFU or WOC	2	(1.6)	3	(2.4)

Abbreviations: CI = confidence interval; *ESR1* = oestrogen receptor 1 gene; *ESR1*-mut-nd = no *ESR1* mutation detected; HR = hazard ratio; IRC = imaging review committee; ITT = intent-to-treat; KM = Kaplan-Meier; LTFU = loss to follow-up; n = number of subjects with the observed group characteristic; N = total number of subjects in group; PFS = progression-free survival; SOC = standard of care; WOC = withdrawal of consent.

[a] The analysis was performed using a stratified Cox proportional hazards model with ties=Efron and the stratification factors: prior treatment with fulvestrant (yes vs no) and presence of visceral metastases (yes vs no); the CI calculated using a profile likelihood method.

[b] The p-value was generated by using a 2-sided stratified log-rank test.

[c] Calculated using KM technique. CI for median PFS is derived based on the Brookmeyer-Crowley method using a linear transformation.

[d] Date of last tumour assessment before missed assessments or date of randomization, whichever is later.

Source: Study 308, Table 14.2.1.1.3

Table 40: Analysis of blinded IRC assessment of PFS rate in ESR1-mut-nd subjects (Study 308 – ITT population)

Time point	**PFS rate[a] (95% CI)**	
	Elacestrant N = 124	**SOC N = 126**
3 months	44.30 (34.98-53.62)	38.92 (29.16-48.67)
6 months	28.58 (18.98-38.18)	21.85 (12.71-30.99)
12 months	18.16 (8.60-27.73)	11.22 (2.82-19.62)
18 months	9.08 (0.00-19.19)	—

Abbreviations: CI = confidence interval; *ESR1* = oestrogen receptor 1 gene; *ESR1*-mut-nd = no *ESR1* mutation detected; IRC = imaging review committee; ITT = intent-to-treat; KM = Kaplan-Meier; N = total number of subjects in group; PFS = progression-free survival; SOC = standard of care.

[a] Calculated using KM technique. CI for PFS is derived based on the Brookmeyer-Crowley method using a linear transformation.

Source: Study 308, Table 14.2.1.1.3

Progression-free survival (investigator assessment)

Discordance was observed in progression between the IRC and investigator assessments in both cohorts (Table 41). Kaplan-Meier plots for investigator assessment of PFS are shown below for all subjects (Figure 17) and *ESR1*-mut subjects (Figure 18).

Among all subjects, 62 subjects (32.6%) in the elacestrant group and 42 subjects (22.7%) in the SOC group were assessed as having PD by the investigators (and will have therefore discontinued treatment) but were not yet considered to have PD by the IRC at the time of assessment of PD by the investigator. In the PFS analysis, these subjects will either be counted as "censored without progression" or, if they subsequently died, to have had a PFS event at the time of death.

Among all subjects, 14 subjects (9.9%) in the elacestrant group and 11 subjects (7.1%) in the SOC group were assessed as having PD by the IRC but will have continued treatment in the absence of an assessment of PD by the investigators.

The analysis of PFS investigator assessment is shown in Table 42 and landmark analysis in Table 43.

In all subjects, the HR for PFS assessed by the investigators was 0.769 (95% CI: 0.625-0.945), stratified log-rank test p = 0.0097.

In *ESR1*-mut subjects, the HR for PFS assessed by the investigators was 0.647 (95% CI: 0.477-0.876), stratified log-rank test p = 0.0049.

Table 41: Analysis of discordance between investigator and IRC tumour assessment of progressive disease (Study 308 - ITT population)

Subjects	All subjects		*ESR1*-mut subjects		*ESR1*-mut-nd subjects[a]	
	Elacestrant N = 239	SOC N = 239	Elacestrant N = 115	SOC N = 113	Elacestrant N = 124	SOC N = 126
Subjects with IRC-assessed PD per RECIST	142	154	60	79	82	75
Subjects with IRC-assessed PD but not PI-assessed PD[b]	14 (9.9)	11 (7.1)	8 (13.3)	8 (10.1)	6 (7.3)	3 (4.0)
Subjects with PI-assessed PD per RECIST	190	185	84	90	106	95
Subjects with PI-assessed PD but not IRC-assessed PD[c]	62 (32.6)	42 (22.7)	32 (38.1)	19 (21.1)	30 (28.3)	23 (24.2)

Abbreviations: *ESR1* = oestrogen receptor 1 gene; *ESR1*-mut = *ESR1* mutation positive; IRC = Imaging Review Committee; ITT = intent-to-treat; N = total number of subjects in group; PD = progressive disease; PFS = progression-free survival; PI = principal investigator; RECIST = Response Evaluation Criteria in Solid Tumours; SOC = standard of care.

[a] *ESR1*-mut-nd values were calculated as subtraction between all subjects and *ESR1*-mut subjects.

[b] Subjects with missing PI response assessment were not included in the no PD category. Percentage was calculated using number of subjects with IRC-assessed PD as denominator.

[c] Subjects with missing IRC response assessment were not included in the no PD category. Percentage was calculated using number of subjects with local PI-assessed PD as denominator.

Source: Study 308, Table 14.2.1.9.1 and Table 14.2.1.9.2

Table 42: Analysis of investigator assessment of PFS (Study 308 - ITT population)

	All subjects				*ESR1*-mut subjects				*ESR1*-mut-nd subjects			
	Elacestrant N = 239		SOC N = 239		Elacestrant N = 115		SOC N = 113		Elacestrant N = 124		SOC N = 126	
HR (95% CI)[a]	0.769 (0.625-0.945)				0.647 (0.477-0.876)				0.892 (0.673-1.183)			
p-value[b]	0.0097				0.0049				0.3596			
Median PFS (months)[c]	2.17		2.00		3.65		2.07		1.94		2.00	
95% CI[c]	1.94-3.58		1.87-2.14		2.10-5.36		1.87-3.48		1.87-3.02		1.87-2.43	
Events, n(%)	192	(80.3)	189	(79.1)	85	(73.9)	90	(79.6)	107	(86.3)	99	(78.6)
Death before progression	5	(2.1)	6	(2.5)	3	(2.6)	1	(0.9)	2	(1.6)	5	(4.0)
Progression	187	(78.2)	183	(76.6)	82	(71.3)	89	(78.8)	105	(84.7)	94	(74.6)
Censored, n(%)	47	(19.7)	50	(20.9)	30	(26.1)	23	(20.4)	17	(13.7)	27	(21.4)
No progression	28	(11.7)	18	(7.5)	20	(17.4)	7	(6.2)	8	(6.5)	11	(8.7)
Progression or death after ≥ 2 missed postbaseline assessments[d]	2	(0.8)	3	(1.3)	0	(0.0)	1	(0.9)	2	(1.6)	2	(1.6)
Progression or death after new anticancer therapy	5	(2.1)	10	(4.2)	3	(2.6)	5	(4.4)	2	(1.6)	5	(4.0)
Alive without postbaseline assessment	7	(2.9)	17	(7.1)	4	(3.5)	10	(8.8)	3	(2.4)	7	(5.6)
LTFU or WOC	5	(2.1)	2	(0.8)	3	(2.6)	0	(0.0)	2	(1.6)	2	(1.6)

Abbreviations: CI = confidence interval; *ESR1* = oestrogen receptor 1 gene; *ESR1*-mut = *ESR1* mutation positive; HR = hazard ratio; ITT = intent-to-treat; KM = Kaplan-Meier; LTFU = loss to follow-up; n = number of subjects with the observed group characteristic; N = total number of subjects in group; PFS = progression-free survival; SOC = standard of care; WOC = withdrawal of consent.

[a] The analysis was performed using a stratified Cox proportional hazards model with ties=Efron and the stratification factors: prior treatment with fulvestrant (yes vs no) and presence of visceral metastases (yes vs no); the CI calculated using a profile likelihood method.

[b] The p-value was generated by using a 2-sided stratified log-rank test.

[c] Calculated using KM technique. CI for median PFS is derived based on the Brookmeyer-Crowley method using a linear transformation.

[d] Date of last tumour assessment before missed assessments or date of randomization, whichever is later.

Source: Study 308, Table 14.2.1.7.1, Table 14.2.1.7.2, and Table 14.2.1.7.3

Figure 17: Kaplan-Meier Plot for investigator assessment of progression-free survival in all subjects (intent-to-treat population)

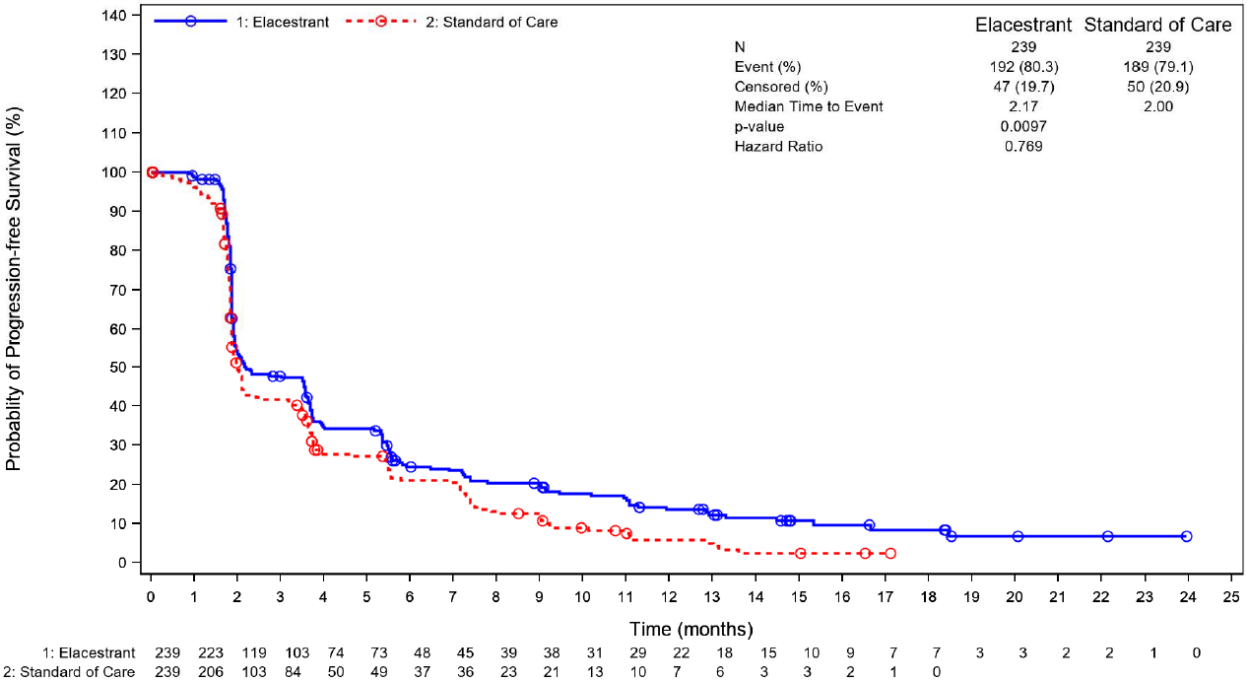
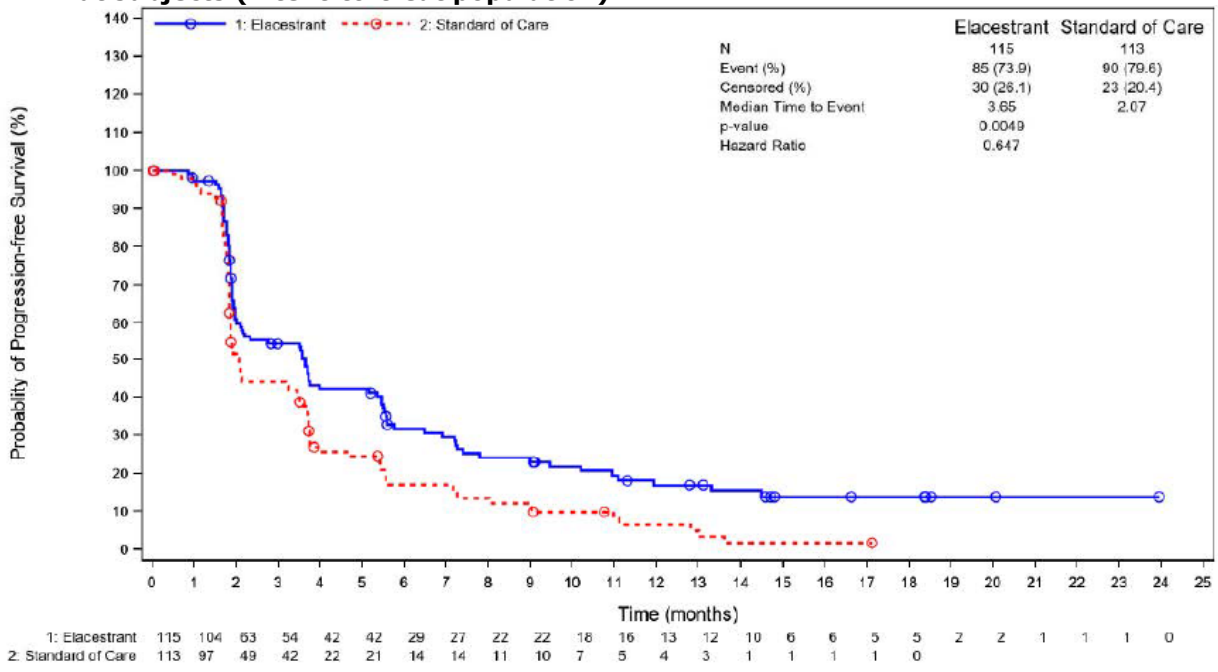


Figure 18: Kaplan-Meier plot for investigator assessment of progression-free survival in ESR1-mut subjects (intent-to-treat population)



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

Table 43: Analysis of PFS rate based on investigator assessment (Study 308 – ITT population)

Time point	PFS rate[a] (95% CI)					
	All subjects		*ESR1*-mut subjects		*ESR1*-mut-nd subjects	
	Elacestrant N = 239	SOC N = 239	Elacestrant N = 115	SOC N = 113	Elacestrant N = 124	SOC N = 126
3 months	47.72 (41.14-54.30)	41.73 (34.99-48.47)	54.24 (44.68-63.79)	43.99 (34.13-53.84)	41.89 (32.95-50.83)	39.72 (30.50-48.94)
6 months	24.52 (18.74-30.29)	20.98 (15.22-26.75)	31.79 (22.66-40.91)	17.10 (9.28-24.93)	18.14 (11.05-25.23)	24.51 (16.18-32.85)
12 months	13.56 (8.74-18.37)	5.75 (2.08-9.41)	16.87 (9.18-24.57)	6.51 (0.93-12.10)	10.71 (4.75-16.66)	5.09 (0.22-9.96)
18 months	8.41 (3.86-12.96)	—	13.81 (6.43-21.18)	—	4.01 (0.00-8.82)	—

Abbreviations: CI = confidence interval; *ESR1* = oestrogen receptor 1 gene; *ESR1*-mut = *ESR1* mutation positive; ITT = intent-to-treat; KM = Kaplan-Meier; N = total number of subjects in group; PFS = progression-free survival; SOC = standard of care.

[a] Calculated using KM technique. CI for PFS is derived based on the Brookmeyer-Crowley method using a linear transformation.

Source: Study 308, Table 14.2.1.7.1, Table 14.2.1.7.2, and Table 14.2.1.7.3

Objective response rate

The ORR as assessed by the blinded IRC in the RE population is shown in Table 44. No subjects had a CR. For *ESR1*-mut-nd subjects, the ORR was 2.1% in the elacestrant group and 4.2% in the SOC group. There was no statistically significant difference in ORR between elacestrant and SOC for any cohort (all subjects, *ESR1*-mut subjects, or *ESR1*-mut-nd subjects).

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

Table 44: Analysis of blinded IRC assessment of ORR (Study 308 - RE population)

	All subjects		*ESR1*-mut subjects	
	Elacestrant N = 179	SOC N = 182	Elacestrant N = 85	SOC N = 86
ORR, n (%)	8 (4.5)	8 (4.4)	6 (7.1)	4 (4.7)
95% CI[a]	1.95-8.62	1.92-8.48	2.63-14.73	1.28-11.48
p-value[b]	0.959		0.499	
BOR, n (%)				
CR (confirmed)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PR (confirmed)	8 (4.5)	8 (4.4)	6 (7.1)	4 (4.7)

	All subjects		*ESR1*-mut subjects	
	Elacestrant N = 179	**SOC N = 182**	**Elacestrant N = 85**	**SOC N = 86**
SD ≥ 6 weeks	75 (41.9)	55 (30.2)	42 (49.4)	22 (25.6)
PD	89 (49.7)	110 (60.4)	32 (37.6)	55 (64.0)
NE	7 (3.9)	9 (4.9)	5 (5.9)	5 (5.8)

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

[a] Binomial Clopper-Pearson 95% CI.

[b] The p-value was generated by using a stratified logistic regression, with the stratification factors of prior treatment with fulvestrant (yes vs no) and presence of visceral metastases (yes vs no).

Source: Study 308, Table 14.2.3.1.4 and Table 14.2.3.1.5

Clinical benefit rate

The CBR as assessed by the blinded IRC in the CBE population is shown in Table 45. There were no subjects with confirmed CR, so the CBR consists of subjects with any BOR of PR or BOR of SD sustained for at least 24 weeks. Among *ESR1*-mut-nd subjects, the CBR was 13.3% in the elacestrant group versus 15.3% in the SOC group.

Table 45: Analysis of blinded IRC assessment of CBR (Study 308 - CBE population)

	All subjects		*ESR1*-mut subjects	
	Elacestrant N = 228	**SOC N = 215**	**Elacestrant N = 108**	**SOC N = 104**
CBR, n (%)	42 (18.4)	29 (13.5)	26 (24.1)	12 (11.5)
95% CI[a]	13.61-24.07	9.22-18.79	16.37-33.25	6.11-19.29
p-value[b]	0.217		0.024	
BOR, n (%)				
CR (confirmed)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PR (confirmed)	8 (3.5)	8 (3.7)	6 (5.6)	4 (3.8)
SD ≥ 24 weeks	34 (14.9)	21 (9.8)	20 (18.5)	8 (7.7)
PD	128 (56.1)	140 (65.1)	53 (49.1)	72 (69.2)
NE[c]	58 (25.4)	46 (21.4)	29 (26.9)	20 (19.2)

Abbreviations: BOR = best overall response; CBE = clinical benefit rate; CBR = clinical benefit rate; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CR = complete response; *ESR1* = oestrogen receptor 1 gene; *ESR1*-mut = *ESR1* mutation positive; IRC = imaging review committee; n = number of subjects with the observed group characteristic; N = total number of subjects in group; NE = not evaluable; OR = overall response; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SD = stable disease; SOC = standard of care.

[a] Binomial Clopper-Pearson 95% CI.

[b] The p-value was generated by using stratified CMH test, with the stratification factors of prior treatment with fulvestrant (yes vs no) and presence of visceral metastases (yes vs no).

[c] NE includes subjects with SD duration between 6 and 24 weeks.

Source: Study 308, Table 14.2.5.1.1 and Table 14.2.5.1.2

Duration of response

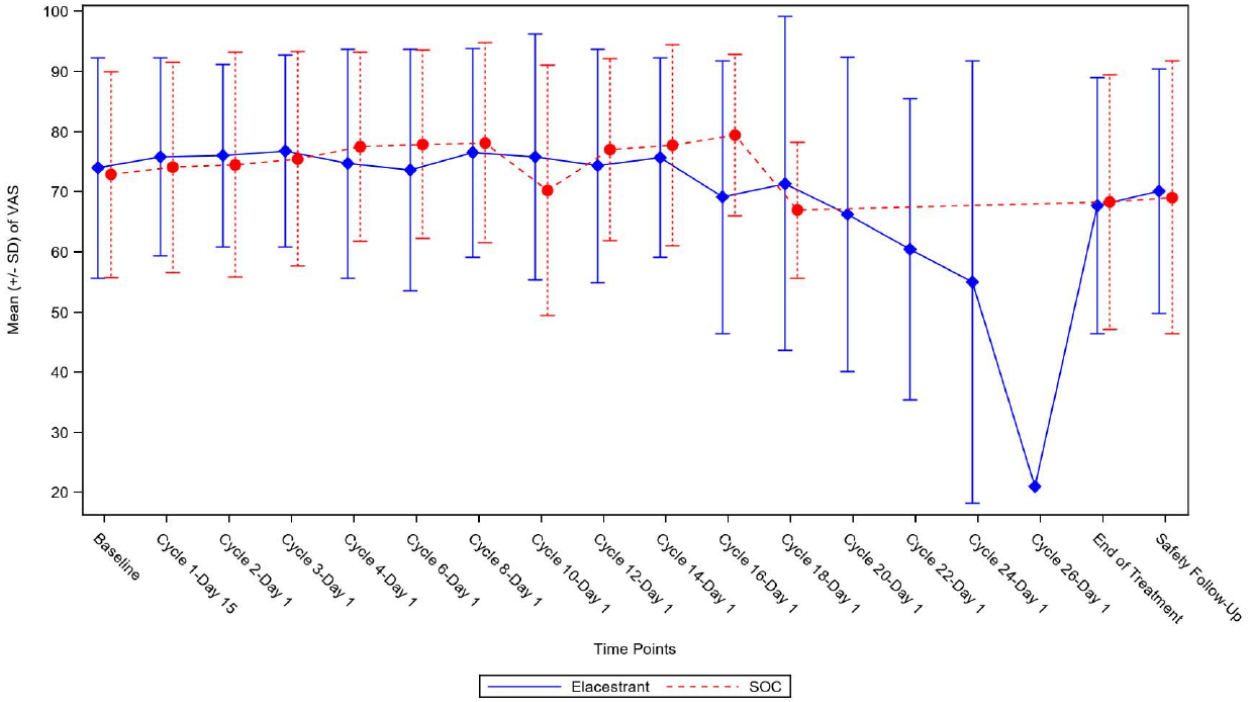
The median DoR as assessed by the blinded IRC could not be calculated in the elacestrant group for either cohort of subjects, as all such subjects were censored without progression or death.

Patient-reported outcomes

EQ-5D-5L and EQ-VAS

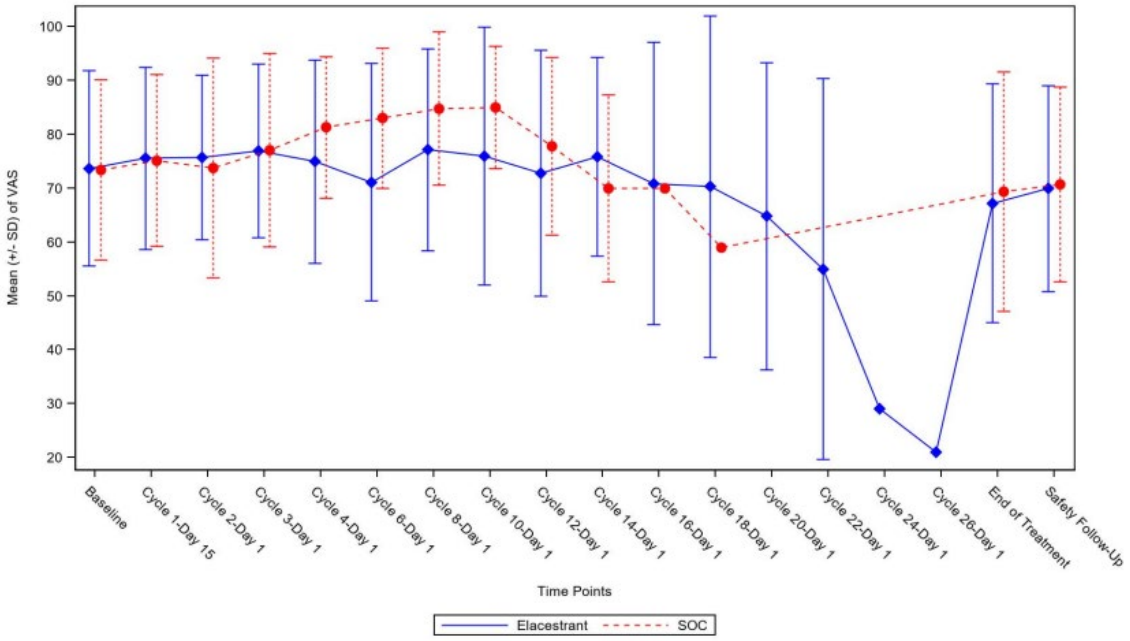
The completion rate for the EQ-5D-5L remained above 70% until Cycle 2 Day 1, but is below 50% after visit Cycle 4 Day 1. EuroQol visual analogue scale (EQ-VAS) results by visit are shown in Figure 19 and Figure 20.

Figure 19: EQ-VAS by visit in all subjects (Study 308 - ITT population)



Abbreviations: EQ-VAS = EuroQol visual analogue scale; ITT = intent-to-treat; SD = standard deviation; SOC = standard of care; VAS = visual analogue scale.
Source: Study 308, Figure 14.2.6.1.2

Figure 20: EQ-VAS by visit in ESR1-mut subjects (Study 308 – ITT population)



Abbreviations: EQ-VAS = EuroQol visual analogue scale; *ESR1* = oestrogen receptor 1 gene; *ESR1*-mut = *ESR1* mutation positive; ITT = intent-to-treat; SD = standard deviation; SOC = standard of care; VAS = visual analogue scale.
Source: Study 308, Figure 14.2.6.1.1

EORTC QLQ-C30

The completion rate for the EORTC QLQ-C30 remained above 70% until Cycle 2 Day 1, but is below 50% after visit Cycle 4 Day 1. There were no noteworthy differences between the treatment groups and no noteworthy changes over time in either group, either for all subjects or *ESR1*-mut subjects based on the mixed model repeated measures (MMRM) analysis of quality of life through Cycle 6 according to the Applicant.

PRO-CTCAE

There were no noteworthy differences between the treatment groups and no noteworthy changes over time in either group for change from baseline in frequency, severity, or interference for any treatment-emergent adverse event, either for all subjects or *ESR1*-mut subjects.

Time to chemotherapy

Among all subjects, chemotherapy as first systemic therapy after treatment discontinuation was recorded for approximately half of the subjects. In the elacestrant group, 114 subjects received chemotherapy after treatment discontinuation (47.7%). In the SOC group, 120 subjects received chemotherapy after treatment discontinuation in the SOC group (50.0%). In the ESR1-mutated population the proportion receiving chemotherapy after treatment discontinuation was 43.5% and 52.2%, in the elacestrant and SOC arm, respectively.

The mean (SD) time to chemotherapy was similar in the elacestrant and SOC groups, at 111.0 (70.14) days and 97.8 (67.28) days, respectively. Subjects with *ESR1*-mut had a time to chemotherapy of 105.8 (63.04) days in the elacestrant group and 102.8 (71.31) days in the SOC group. Subjects with *ESR1*-mut-nd had a time to chemotherapy of 115.0 (75.46) days in the elacestrant group and 92.9 (63.36) days in the SOC group. Some subjects may have received therapy other than chemotherapy as their first post-study therapy. Time from randomisation to first new anti-cancer therapy in the

overall population was at median 92.0 days in the elacestrant arm and 77.5 days in the SOC arm.

- **Ancillary analyses**

Restricted mean survival time (RMST)

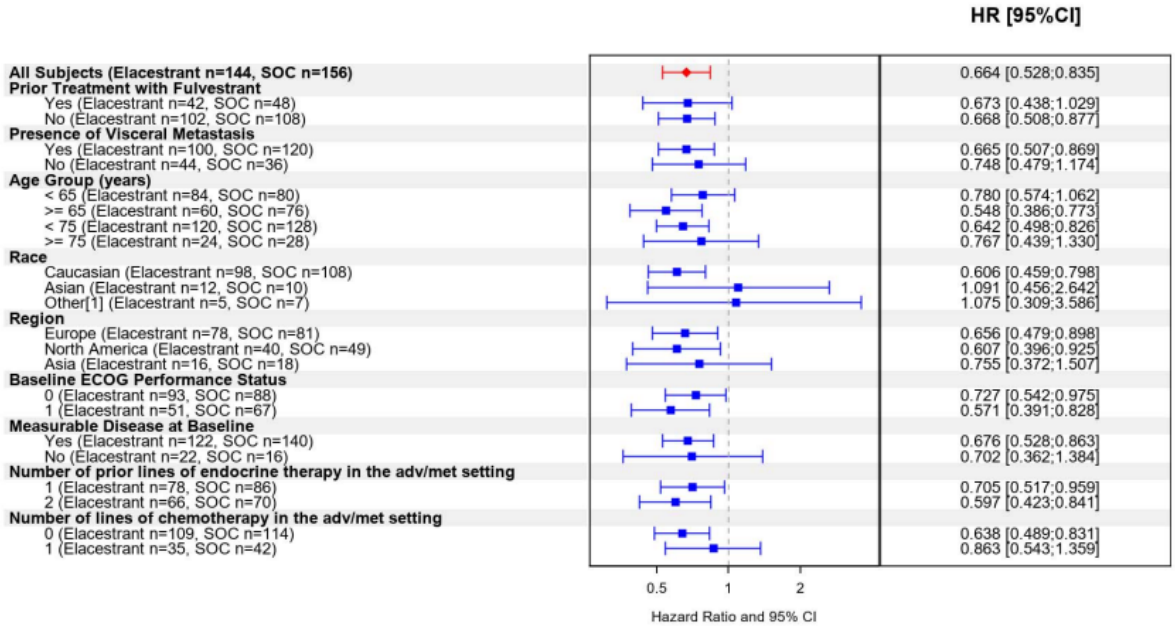
In all patients, restricted mean survival time (RMST) was 7.54 (SE 0.85) in the elacestrant arm and 5.18 (SE 0.50) in the SOC arm. RMST difference was 2.36 (95% CI: 0.59-4.13), p-value 0.0088.

For ESR1-mutated patients, restricted mean survival time (RMST) was 9.25 (SE 1.15) in the elacestrant arm and 5.17 (SE 0.87) in the SOC arm. RMST difference was 4.08 (95% CI: 1.57-6.59), p-value 0.0015.

Subgroup analyses

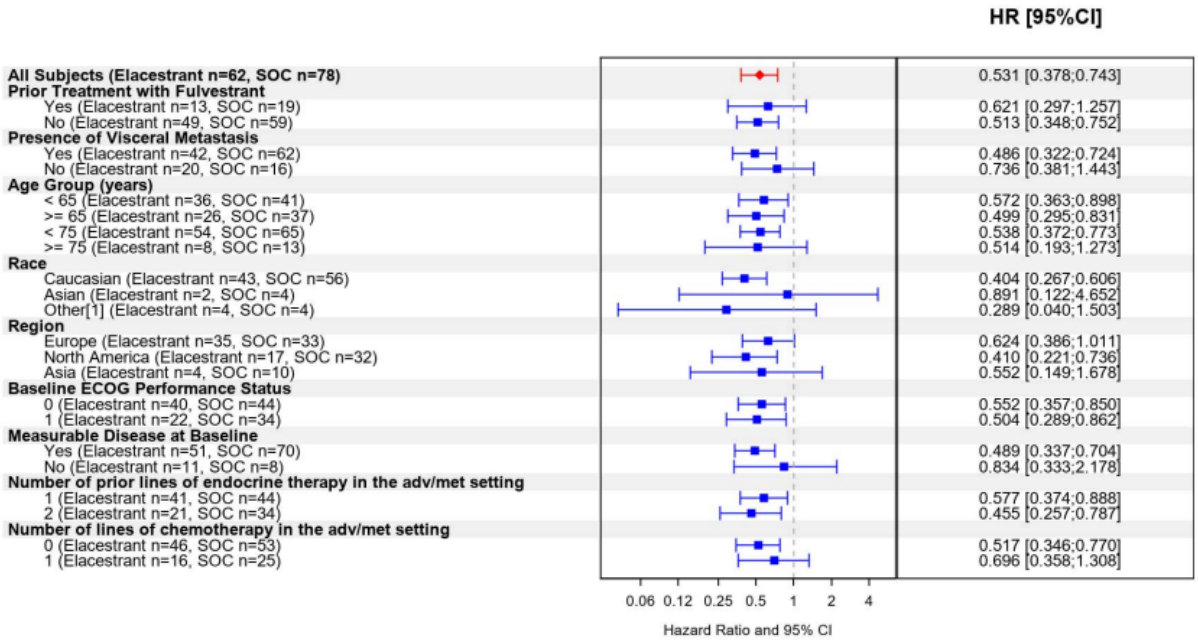
Prespecified subgroup analyses were conducted and displayed by forest plot for all subjects (Figure 21) and *ESR1*-mut subjects (Figure 22).

Figure 21: Forest plot of blinded IRC assessment of PFS in all subjects (N = 478) (Study 308 - ITT Population)



Abbreviations: adv/met = advanced/metastatic; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; IRC = imaging review committee; ITT = intent-to-treat; n = number of PFS events; PFS = progression-free survival; SOC = standard of care.
[1] Includes subjects with multiple races.
HR is calculated using an unstratified Cox proportional hazards model with ties = Efron. The CI is calculated using a profile likelihood approach.
Source: Study 308, Figure 14.2.1.3.2
The "n's" displayed in the following plots represent the number of events in each subgroup and treatment (rather than the number of subjects) due to the limited space in the figures.

Figure 22: Forest plot of blinded IRC assessment of PFS in ESR1-mut subjects (N = 228) (Study 308 - ITT Population)



Abbreviations: adv/met = advanced/metastatic; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; *ESR1*-mut = *ESR1* mutation positive; HR = hazard ratio; IRC = imaging review committee; ITT = intent-to-treat; n = number of PFS events; PFS = progression-free survival; SOC = standard of care.
[1] Includes subjects with multiple races.
HR is calculated using an unstratified Cox proportional hazards model with ties = Efron. The CI is calculated using a profile likelihood approach.
Source: Study 308, Figure 14.2.1.3.1
The "n's" displayed in the following plots represent the number of events in each subgroup and treatment (rather than the number of subjects) due to the limited space in the figures.

Prior treatment with fulvestrant

The subgroup analysis of the blinded IRC assessment of PFS for subjects with and without prior treatment with fulvestrant (one of the stratification factors) is shown in Table 46. KM plots of PFS for subjects with and without prior treatment with fulvestrant are shown in Figure 23 (for all subjects) and in Figure 24 (for ESR1-mut subjects).

Table 46: Subgroup analysis of blinded IRC assessment of PFS by prior treatment with Fulvestrant (Study 308 - ITT Population)

Prior treatment with fulvestrant	All subjects		*ESR1*-mut subjects	
	Elacestrant N = 239	SOC N = 239	Elacestrant N = 115	SOC N = 113
Yes				
HR (95% CI)[a]	0.673 (0.438-1.029)		0.621 (0.297-1.257)	
Median PFS[b]	1.91	1.87	1.91	2.14
95% CI[b]	1.87-2.33	1.87-2.14	1.91-7.79	1.87-3.75
Events/subjects	42/70	48/75	13/27	19/28
No				
HR (95% CI)[a]	0.668 (0.508-0.877)		0.513 (0.348-0.752)	

Prior treatment with fulvestrant	All subjects		*ESR1*-mut subjects	
	Elacestrant N = 239	SOC N = 239	Elacestrant N = 115	SOC N = 113
Median PFS[b]	3.65	1.94	4.14	1.87
95% CI[b]	2.17-5.32	1.87-3.45	2.20-8.61	1.84-2.10
Events/subjects	102/169	108/164	49/88	59/85

Abbreviations: CI = confidence interval; *ESR1* = oestrogen receptor 1 gene; *ESR1*-mut = *ESR1* mutation positive; HR = hazard ratio; IRC = imaging review committee; ITT = intent-to-treat; KM = Kaplan-Meier; N = total number of subjects in group; PFS = progression-free survival; SOC = standard of care.

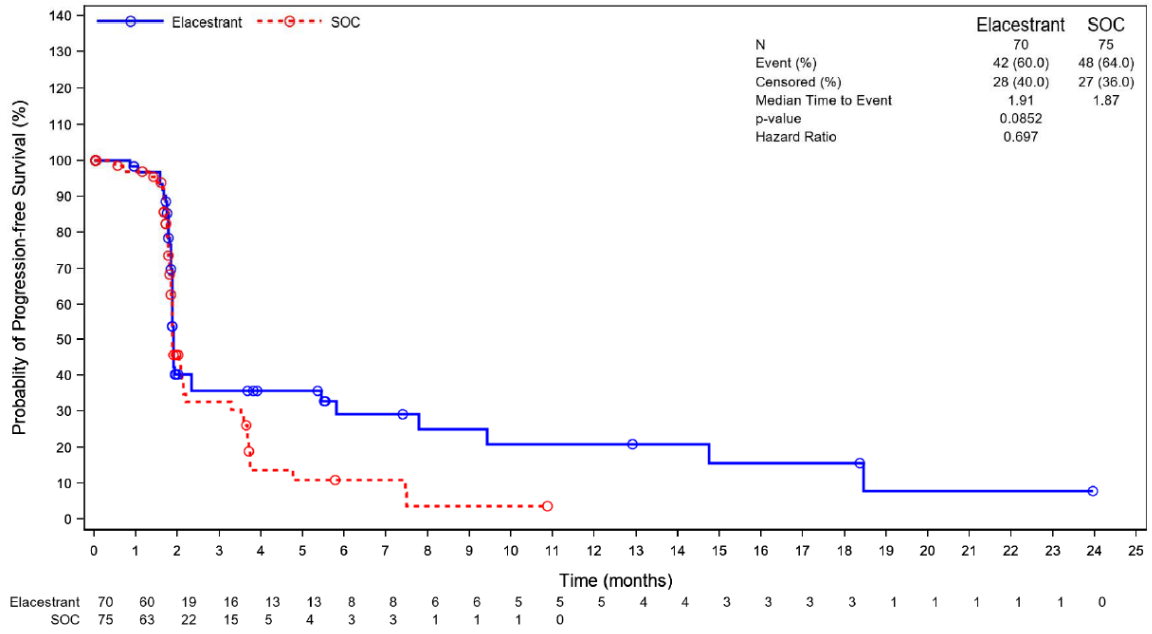
[a] HR is calculated using an unstratified Cox proportional hazards model with ties= Efron. The CI is calculated using a profile likelihood approach.

[b] Calculated using KM technique. CI for median PFS is derived based on the Brookmeyer-Crowley method using a linear transformation.

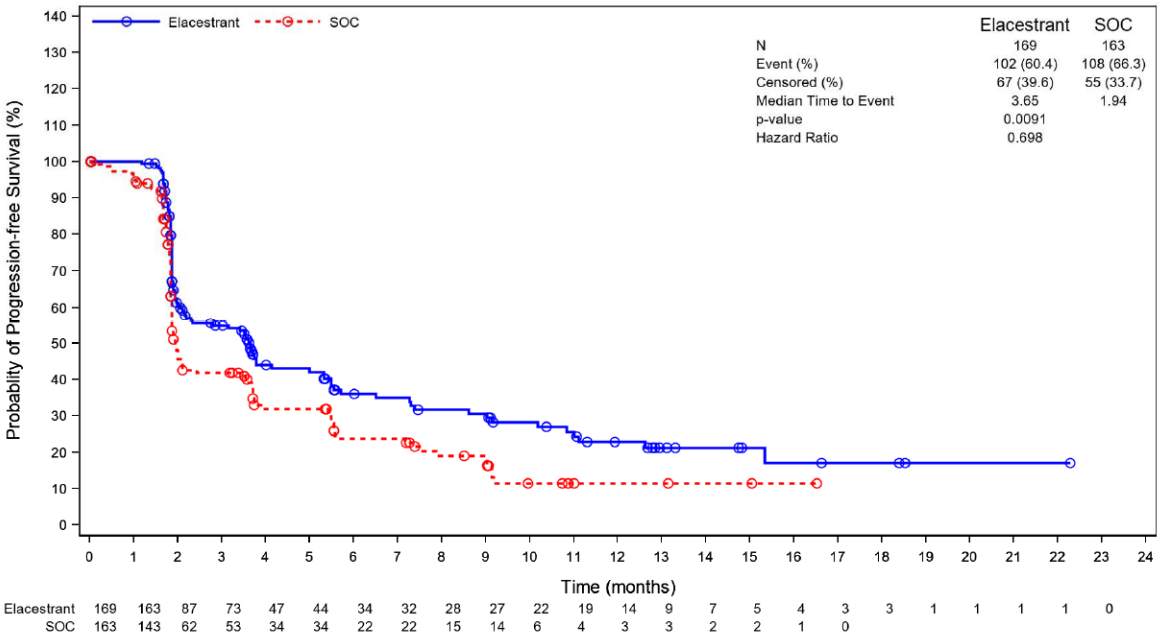
Source: Study 308, Table 14.2.1.8.1, Table 14.2.1.8.2

Figure 23 Kaplan-Meier plot for blinded IRC assessment of PFS in all subjects with and without prior treatment with Fulvestrant (Study 308 – ITT Population)

With Prior Fulvestrant



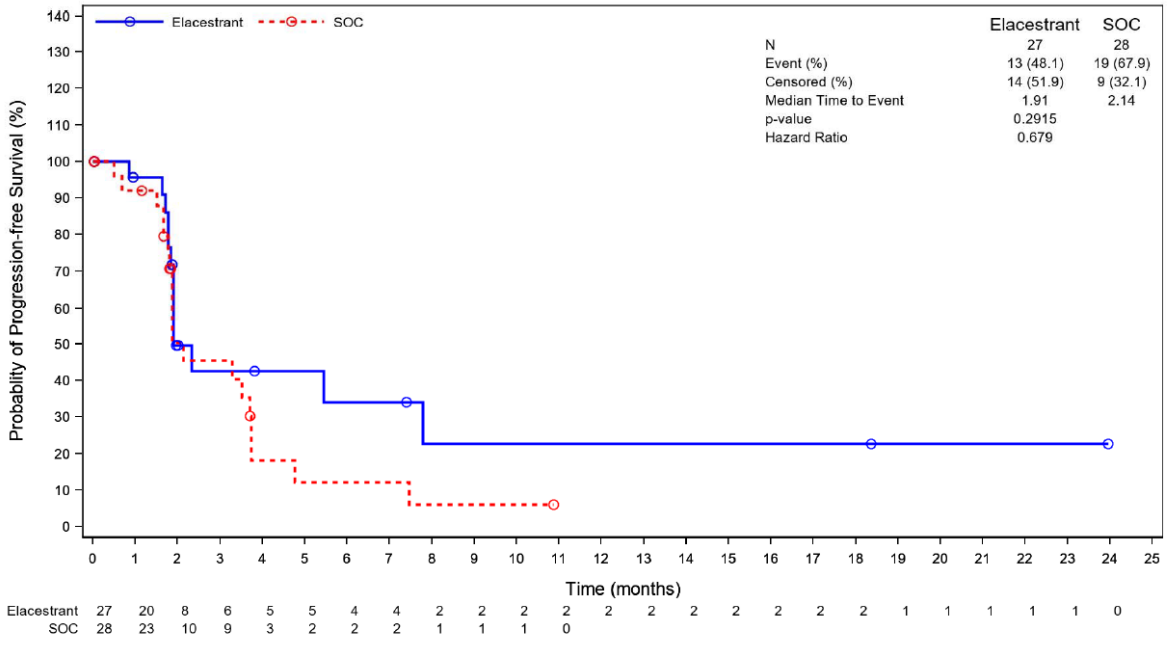
Without Prior Fulvestrant



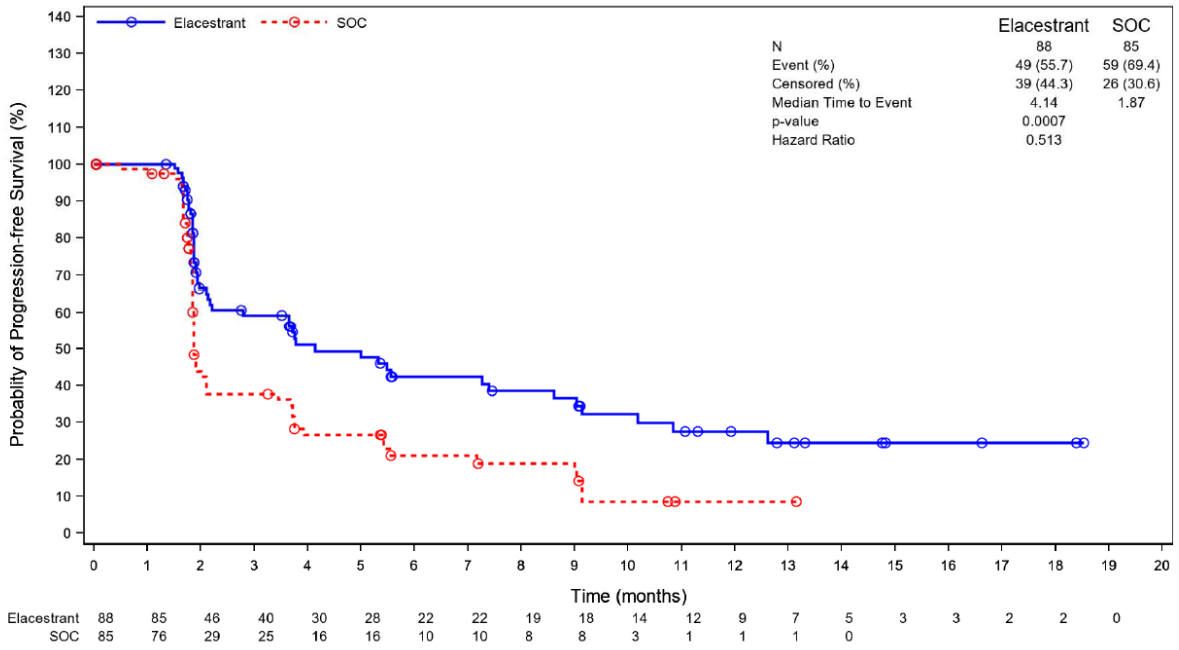
Abbreviations: IRC = imaging review committee; ITT = intent-to-treat; KM = Kaplan-Meier; N = total number of subjects in group; PFS = progression-free survival; SOC = standard of care.
HR is calculated using a stratified Cox proportional hazards model.
Source: Study 308, Figures 14.2.1.5.2, 14.2.1.5.4

Figure 24: Kaplan-Meier plot for blinded IRC assessment of PFS in ESR1-mut subjects with and without prior treatment with fulvestrant (Study 308 – ITT population)

With Prior Fulvestrant



Without Prior Fulvestrant



Abbreviations: *ESR1* = oestrogen receptor 1 gene; *ESR1*-mut = *ESR1* mutation positive; IRC = imaging review committee; ITT = intent-to-treat; KM = Kaplan-Meier; N = total number of subjects in group; PFS = progression-free survival; SOC = standard of care.
HR is calculated using a stratified Cox proportional hazards model.
Source: Study 308, Figures 14.2.1.5.1, 14.2.1.5.3

Post hoc supportive analysis of the primary endpoint

Additional post hoc supportive analyses were conducted for PFS comparing elacestrant to fulvestrant and AIs.

Elacestrant versus fulvestrant:

Among all subjects, 166 out of 239 subjects (69%) received fulvestrant as the SOC treatment in this study, and the HR for this analysis was 0.684 (95% CI: 0.521-0.897). The IRC-assessed PFS estimates at the various time points are presented below.

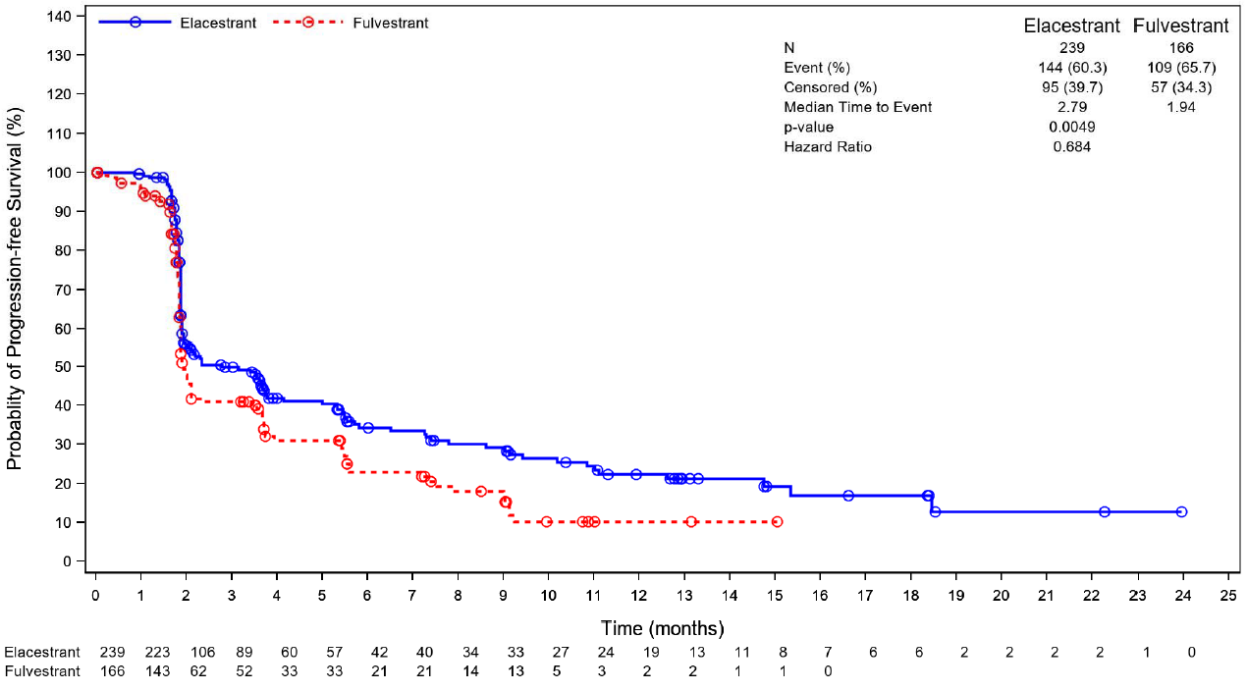
At 3 months: 49.75% in the elacestrant group versus 40.86% in the SOC group

At 6 months: 34.32% in the elacestrant group versus 22.86% in the SOC group

At 12 months: 22.32% in the elacestrant group versus 10.15% in the SOC group

At 18 months: 16.82% in the elacestrant group versus "data not available" in the SOC group

Figure 25: Kaplan-Meier plot of progression-free survival for elacestrant vs fulvestrant, in all subjects assessed by blinded Imaging Review Committee (intent-to-treat population)



Source: Study 308, Figure 14.2.1.4.2

Among *ESR1*-mut subjects, 83 out of 113 subjects (73%) received fulvestrant as the SOC treatment in this study, and the HR for this analysis was 0.504 (95% CI: 0.341-0.741). The IRC-assessed PFS estimates at the various time points are presented below.

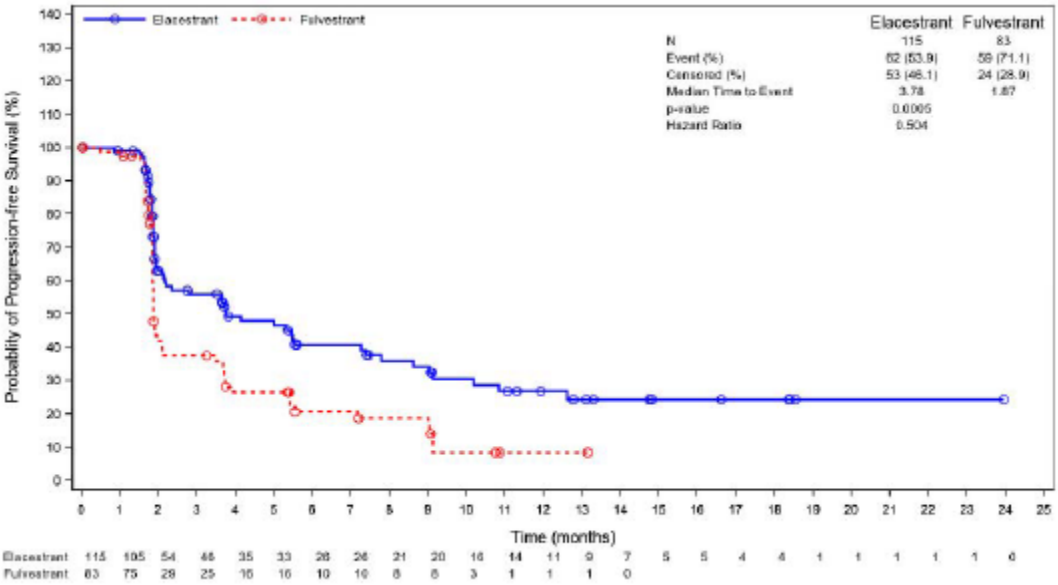
At 3 months: 55.93% in the elacestrant group versus 37.42% in the SOC group

At 6 months: 40.76% in the elacestrant group versus 20.75% in the SOC group

At 12 months: 26.76% in the elacestrant group versus 8.41% in the SOC group

At 18 months: 24.33% in the elacestrant group versus "data not available" in the SOC group

Figure 26: Kaplan-Meier plot of progression-free survival for elacestrant vs fulvestrant, in ESR1-mut subjects assessed by blinded Imaging Review Committee (intent-to-treat population)



Among *ESR1*-mut-nd subjects, 83 out of 126 subjects (66%) received fulvestrant. The HR for progression under elacestrant versus fulvestrant treatment was 0.925 (95% CI: 0.631 to 1.363), stratified log-rank test p-value = 0.6224. The 6- and 12-months PFS rates were 28.58% and 18.16% versus 25.43% and 12.87%, respectively.

Elacestrant versus AIs:

Among all subjects, 73 out of 239 subjects (31%) received an AI as the SOC treatment in this study, and the HR for this analysis was 0.779 (95% CI: 0.520-1.172). Median PFS was 2.79 months (95% CI: 1.94-3.78) in the elacestrant group and 1.87 months (95% CI: 1.87-2.20) in the AI group. The IRC-assessed PFS estimates at the various time points are presented below.

At 3 months: 49.75% in the elacestrant group versus 35.04% in the AI group

At 6 months: 34.32% in the elacestrant group versus 13.35% in the AI group

At 12 months: 22.32% in the elacestrant group versus 6.67% in the AI group

At 18 months: 16.82% in the elacestrant group versus "data not available" in the AI group

Among *ESR1*-mut subjects, 30 out of 113 subjects (27%) received an AI, and the HR was 0.659 (95% CI: 0.320-1.329). Median PFS was 3.78 months (95% CI: 2.17-7.26) in the elacestrant group and 2.14 months (95% CI: 1.87-3.75) in the AI group. The IRC-assessed PFS estimates at the various time points are presented below.

At 3 months: 55.93% in the elacestrant group versus 46.17% in the AI group

At 6 months: 40.76% in the elacestrant group versus 12.31% in the AI group

At 12 months: 26.76% in the elacestrant group versus "data not available" in the AI group

At 18 months: 24.33% in the elacestrant group versus "data not available" in the AI group

Sensitivity analysis for PFS in the ESR1-mut population with and without prior fulvestrant by type of SOC treatment (fulvestrant or AI) are reported below (Table 47, Table 48).

Table 47: Progression-free survival for elacestrant vs SOC, in ESR1-mut patients with prior fulvestrant, assessed by blinded Imaging Review Committee (IRC) (intent-to-treat population)

	Elacestrant (N = 27)	AI (N = 27)
Events, n (%)	13 (48.1)	18 (66.7)
Death without documented progression	1 (3.7)	1 (3.7)
Documented progression	12 (44.4)	17 (63)
Censored subjects, n (%)	14 (51.9)	9 (33.3)
Censored progression or death after missing ≥ 2 consecutive post-baseline tumor assessments [1]	2 (7.4)	1 (3.7)
Censored progression or death after taking new anti-cancer therapies	1 (3.7)	3 (11.1)
Lost to follow-up or withdrew consent before documented progression or death	0 (0)	1 (3.7)
No documented progression and no death (with a post-baseline tumor assessment)	8 (29.6)	3 (11.1)
No post-baseline assessments and no death	3 (11.1)	1 (3.7)
Median PFS (months) [2]	1.91	2.14
95% CI for median progression-free survival [2]	1.91 - 7.79	1.87 - 3.75
Q1 (95% CI)	1.84 (1.71 - 1.91)	1.81 (1.51 - 1.87)
Q3 (95% CI)	7.79 (2.33 - NC)	3.75 (3.29 - 7.46)
Min, Max	0.03+, 23.95+	0.03+, 10.87+
PFS rate at 3 months (95% CI) [2]	42.57 (19.47 - 65.67)	47.39 (25.52 - 69.26)
PFS rate at 6 months (95% CI) [2]	34.06 (10.30 - 57.81)	12.64 (0.00 - 28.52)
PFS rate at 12 months (95% CI) [2]	22.70 (0.00 - 46.80)	-
PFS rate at 18 months (95% CI) [2]	22.70 (0.00 - 46.80)	-
Hazard ratio [3]	0.705	-
95% CI for Hazard ratio [3]	0.334 - 1.447	-
2-sided p-value [4]	0.3465	-

+: Censored,
Abbreviations: AI = Aromatase inhibitor; SOC = Standard of Care, ESR1-mut = ESR1 mutation, CI = Confidence Interval, Q1 = First Quartile, Q3 = Third Quartile, PFS = Progression-free survival,
NC = Not calculable, SE = Standard Error.
Progression is determined according to assessment by blinded IRC.
PFS is defined as the time from the date of randomization until the date of objective disease progression or death (by any cause in the absence of progression). For subjects, without objective disease progression or death, PFS will be censored according to SAP Section 4.7.1.1.
[1] Date of last tumor assessment before missed assessments or date of randomization, whichever is later.
[2] Calculated using Kaplan-Meier technique. CI for 25th, 50th (median) and 75th percentiles of PFS are derived based on the Brookmeyer-Crowley method using a linear transformation.
[3] The analysis was performed using a stratified Cox Proportional Hazards model with ties = Efron and the stratification factors: presence of visceral metastases (yes vs
no); the CI calculated using a profile likelihood approach.
[4] The p-value was generated by using a two-sided stratified log-rank test.
Data cut-off: 06 September 2021.
Source: EMERALD EMA Request, Table 14.1.1, Annex A.

Table 48: Progression-free survival for elacestrant vs SOC, in ESR1-mut patients with no prior fulvestrant, assessed by blinded Imaging Review Committee (IRC) (intent-to-treat population)

	Elacestrant (N = 88)	Fulvestrant (N = 82)
Events, n (%)	49 (55.7)	58 (70.7)
Death without documented progression	2 (2.3)	0 (0)
Documented progression	47 (53.4)	58 (70.7)
Censored subjects, n (%)	39 (44.3)	24 (29.3)
Censored progression or death after missing ≥ 2 consecutive post-baseline tumor assessments [1]	3 (3.4)	1 (1.2)

	Elacestrant (N = 88)	Fulvestrant (N = 82)
Censored progression or death after taking new anti-cancer therapies	2 (2.3)	1 (1.2)
Lost to follow-up or withdrew consent before documented progression or death	2 (2.3)	0 (0)
No documented progression and no death (with a post-baseline tumor assessment)	31 (35.2)	16 (19.5)
No post-baseline assessments and no death	1 (1.1)	6 (7.3)
Median PFS (months) [2]	4.14	1.87
95% CI for median progression-free survival [2]	2.20 - 8.61	1.84 - 2.10
Q1 (95% CI)	1.87 (1.84 - 2.14)	1.81 (1.74 - 1.84)
Q3 (95% CI)	12.62 (8.61 - NC)	5.42 (3.45 - 9.03)
Min, Max	0.03+, 18.53+	0.03+, 13.14+
PFS rate at 3 months (95% CI) [2]	59.15 (47.95 - 70.34)	37.93 (26.40 - 49.47)
PFS rate at 6 months (95% CI) [2]	42.42 (30.49 - 54.35)	21.04 (10.84 - 31.23)
PFS rate at 12 months (95% CI) [2]	27.60 (15.75 - 39.46)	8.52 (0.22 - 16.82)
PFS rate at 18 months (95% CI) [2]	24.54 (12.57 - 36.50)	-
Hazard ratio [3]	0.516	-
95% CI for Hazard ratio [3]	0.349 - 0.760	-
2-sided p-value [4]	0.0008	-

+: Censored,
Abbreviations: SOC = Standard of Care, ESR1-mut = ESR1 mutation, CI = Confidence Interval, Q1 = First Quartile, Q3 = Third Quartile, PFS = Progression-free survival, NC = Not calculable, SE = Standard Error.
Progression is determined according to assessment by blinded IRC.
PFS is defined as the time from the date of randomization until the date of objective disease progression or death (by any cause in the absence of progression). For subjects without objective disease progression or death, PFS will be censored according to SAP Section 4.7.1.1.
[1] Date of last tumor assessment before missed assessments or date of randomization, whichever is later.
[2] Calculated using Kaplan-Meier technique. CI for 25th, 50th (median) and 75th percentiles of PFS are derived based on the Brookmeyer-Crowley method using a linear transformation.
[3] The analysis was performed using a stratified Cox Proportional Hazards model with ties = Efron and the stratification factors: presence of visceral metastases (yes vs
no); the CI calculated using a profile likelihood approach.
[4] The p-value was generated by using a two-sided stratified log-rank test.
Data cut-off: 06 September 2021.
Source: EMERALD EMA Request, Table 14.1.2, Annex A.

Among *ESR1*-mut-nd subjects, 43 out of 126 subjects (34%) received an AI. The HR for progression elacestrant versus AI treatment was 0.848 (95% CI: 0.517 to 1.409), stratified log-rank test p-value = 0.4763.

PFS by duration of CDK4/6i in patients with *ESR1*-mut:

An exploratory post-hoc analysis examined the PFS of elacestrant, relative to standard of care, according to the duration of prior treatment with CDK4/6 inhibitors plus endocrine therapy in the metastatic setting (Table 49).

Table 49: PFS by duration of CDK4/6i in patients with ESR1 mutations

	Elacestrant	SoC
Duration on prior CDK4/6i		
• ≥ 6 months, n	103	102
Median PFS (mo)	4.14	1.87
Hazard ratio, 95% CI	0.52 (0.36-0.75)	
• ≥ 12 months, n	78	81
Median PFS (mo)	8.61	1.91
Hazard ratio, 95% CI	0.41 (0.26-0.64)	
• ≥ 18 months, n	55	56
Median PFS (mo)	8.61	2.1
Hazard ratio, 95% CI	0.48 (0.27-0.83)	

Source: EMERALD EMA Request, Table 30.2.1-3, Annex A

PFS per type of *ESR1* mutation:

In Table 50 below, a list of the mutations in ESR1 sequenced on patient's ctDNA is described with the median PFS if possible with the number of cases.

Table 50: Median PFS for each variant detected by Guardant360 CDx (within the proposed biomarker definition) and regardless of the number of mutations detected in that subject

	Elacestrant			Standard of Care		
Mutation	**# patients**	**# events**	**Median PFS^**	**# patients**	**# events**	**Median PFS^**
D538G	70	36	4.140	68	52	1.873
Y537S	49	25	3.647	39	25	1.873
Y537N	34	19	4.140	30	23	1.938
E380Q	15	9	3.778	15	9	2.103
L536H	7	5	4.994	9	8	3.745
Y537C	7	4	7.261	7	4	1.922
L536P	5	2	NA	4	3	NA
L536R	3	1	NA	4	2	NA
S463P	3	3	NA	4	3	NA
H524L	2	2	NA	2	2	NA
M543L	2	1	NA	0	0	NA
Y537D	2	0	NA	2	1	NA
D351H	1	1	NA	0	0	NA
D351N	1	1	NA	0	0	NA
E380K	0	0	NA	1	1	NA
E397D	1	1	NA	0	0	NA
E542D	1	1	NA	0	0	NA
E542Q	1	1	NA	0	0	NA
F404I	0	0	NA	1	1	NA
F404V	0	0	NA	1	1	NA
F404L	0	0	NA	2	2	NA
H356D	1	1	NA	1	0	NA
H356Y	1	1	NA	0	0	NA
L370F	1	1	NA	0	0	NA
L379I	0	0	NA	1	1	NA
L536Q	1	1	NA	0	0	NA
L536V	0	0	NA	1	0	NA
L539V	1	1	NA	0	0	NA
L539H	1	1	NA	0	0	NA
L541P	1	1	NA	0	0	NA
M342L	1	1	NA	0	0	NA
M343I	0	0	NA	1	1	NA
M357I	0	0	NA	1	1	NA
M421L	0	0	NA	2	2	NA
M543T	1	1	NA	0	0	NA
P535S	1	1	NA	0	0	NA
R503Q	1	1	NA	0	0	NA
R503W	0	0	NA	1	1	NA
S329A	1	0	NA	0	0	NA
V392I	1	1	NA	0	0	NA
V533M	0	0	NA	1	1	NA
V534G	1	0	NA	0	0	NA
V534L	0	0	NA	1	1	NA
Y537H	0	0	NA	1	1	NA

Abbreviations: NA = not applicable; PFS = progression-free survival.
NA: not applicable, when the number of patients in the corresponding category is 6 or less.
Source: EMERALD EMA Request, Table 28, Annex A.

Updated efficacy analyses with data cut-off date 02 September 2022: *PFS*

An update of the PFS analyses with a data cut-off date of 02 September 2022, providing approximately one additional year of data, was conducted. At that time only 7 additional PFS events were observed, leading to a total of 307 events, relative to the original cut-off date of 06 September 2021. The following tables show the results of the updated PFS analysis for all patients and ESR1-mut patients, based on a cut-off date of 02 September 2022. At this cut-off, median follow-up in the study was 20.4 months for all patients and for ESR1 mut patients. For PFS median follow-up was 24.0 months.

Table 51 Blinded Imaging Review Committee (IRC): Final PFS analysis (cut-off date of 06 September 2021) and updated PFS analysis (cut-off date of 02 September 2022)- ITT population

	Final PFS analysis		**Updated PFS analysis**	
	Elacestrant (N = 239)	**SoC (N = 239)**	**Elacestrant (N = 239)**	**SoC (N = 239)**
Total number of PFS events	144	156	149	158
Hazard ratio	0.697		0.696	
(95% CI)	0.552-0.880		0.552-0.876	
2-sided p-value	0.0018		0.0015	

Abbreviations: CI = confidence interval; PFS = progression-free survival; SoC = standard of care.
* The p-value was generated by using a two-sided stratified log-rank test.
Source: Study 308 CSR, Table 14.2.1.1.2; EMERALD EMA Request, Table 3.1.2, Annex A.

Table 52 Blinded Imaging Review Committee (IRC): Final PFS analysis (cut-off date of 06 September 2021) and updated PFS analysis (cut-off date of 02 September 2022)- ERS1-mut population

	Final PFS analysis		**Updated PFS analysis**	
	Elacestrant (N = 115)	**SoC (N = 113)**	**Elacestrant (N = 115)**	**SoC (N = 113)**
Total number of PFS events	62	78	67	80
Hazard ratio	0.546		0.543	
(95% CI)	0.387-0.768		0.387-0.759	
2-sided p-value	0.005		0.0004	

Abbreviations: CI = confidence interval; PFS = progression-free survival; SoC = standard of care.
* The p-value was generated by using a two-sided stratified log-rank test.
Source: Study 308 CSR, Table 14.2.1.1.1; EMERALD EMA Request, Table 3.1.1, Annex A.

PFS<7weeks

The tables below provide a summary of patients who had a progression event <7 weeks as assessed by the Blinded Imaging Review Committee, for All patients and *ESR1*-mut patients.

Table 53: Frequency table for PFS <7 weeks, in all patients assessed by blinded Imaging Review Committee (IRC)

Intent-to-Treat Population (N = 478)				
Description	**Description**	**Elacestrant (N = 24)**	**SOC (N = 46)**	**Overall (N = 70)**
All censored	All censored	17 (70.8%)	30 (65.2%)	47 (67.1%)
	Censored progression or death after missing ⩾ 2 consecutive post-baseline tumor assessments	1 (5.9%)	2 (6.7%)	3 (6.4%)
	Censored progression or death after taking new anti-cancer therapies	5 (29.4%)	8 (26.7%)	13 (27.7%)
	Lost to follow-up or withdrew consent before documented progression or death	1 (5.9%)	0 (0%)	1 (2.1%)
	No baseline measurable or evaluable lesion	1 (5.9%)	1 (3.3%)	2 (4.3%)
	No documented progression and no death (with a post-baseline tumor assessment)	3 (17.6%)	4 (13.3%)	7 (14.9%)
	No post-baseline assessments and no death	6 (35.3%)	15 (50%)	21 (44.7%)
N patients censored for IRC but events for Investigator [1]	All patients censored for IRC but events for Investigator [1]	2 (11.8%)	7 (23.3%)	9 (19.1%)
All events	All events	7 (29.2%)	16 (34.8%)	23 (32.9%)
	Death without documented progression [2]	2 (28.6%)	3 (18.8%)	5 (21.7%)
	Documented progression [2]	5 (71.4%)	13 (81.3%)	18 (78.3%)

Abbreviations: SOC = Standard of Care.
[1] Total number of censored patients with PFS <7 weeks assessed by IRC is used as denominator for the calculatio n of the percentages for each arm.
[2] Total number of patients experienced an event with PFS <7 weeks assessed by IRC is used as denominator for t he calculation of the percentages for each arm.
Data cut-off: 06 September 2021.
Source: EMERALD EMA Request, Table 13.1.1, Annex A.

Table 54: Frequency table for PFS < 7 weeks, in ESR1-mut patients assessed by blinded Imaging Review Committee (IRC)

Intent-to-Treat Population (N = 478)				
Description	**Description**	**Elacestrant (N = 13)**	**SOC (N = 20)**	**Overall (N = 33)**
All censored	All censored	10 (76.9%)	14 (70%)	24 (72.7%)
	Censored progression or death after missing ≥2 consecutive post-baseline tumor assessments	1 (10%)	0 (0%)	1 (4.2%)
	Censored progression or death after taking new anti-cancer therapies	2 (20%)	3 (21.4%)	5 (20.8%)
	No documented progression and no death (with a post-baseline tumor assessment)	3 (30%)	3 (21.4%)	6 (25%)
	No post-baseline assessments and no death	4 (40%)	8 (57.1%)	12 (50%)
N patients censored for IRC but events for Investigator [1]	All patients censored for IRC but events for Investigator [1]	1 (10%)	3 (21.4%)	4 (16.7%)
All events	All events	3 (23.1%)	6 (30%)	9 (27.3%)
	Death without documented progression [2]	2 (66.7%)	0 (0)	2 (22.2%)
	Documented progression [2]	1 (33.3%)	6 (100)	7 (77.8%)

Abbreviations: SOC = Standard of Care, ESR1-mut = ESR1 mutation.
[1] Total number of censored patients with PFS <7 weeks assessed by IRC is used as denominator for the calculatio n of the percentages for each arm.
[2] Total number of patients experienced an event with PFS <7 weeks assessed by IRC is used as denominator for the calculation of the percentages for each arm.
Data cut-off: 06 September 2021.
Source: EMERALD EMA Request, Table 13.1.2, Annex A.

The tables below provide a summary of subjects who achieved PFS < 7 weeks as assessed by the Investigator for All patients and ESR1-mut patients, respectively.

Table 55 Frequency table for PFS < 7 weeks, in all patients assessed by investigator

Intent-to-Treat Population (N = 478)				
Description	**Description**	**Elacestrant (N = 23)**	**SOC (N = 45)**	**Overall (N = 68)**
Censored	All censored	16 (69.6%)	25 (55.6%)	41 (60.3%)
	Censored progression or death after missing ≥ 2 consecutive post-baseline tumor assessments	1 (6.3%)	0 (0%)	1 (2.4%)
	Censored progression or death after taking new anti-cancer therapies	5 (31.3%)	8 (32%)	13 (31.7%)
	Lost to follow-up or withdrew consent before documented progression or death	1 (6.3%)	0 (0%)	1 (2.4%)
	No documented progression and no death (with a post-baseline tumor assessment)	2 (12.5%)	0 (0%)	2 (4.9%)
	No post-baseline assessments and no death	7 (43.8%)	17 (68%)	24 (58.5%)
N patients censored for Investigator but events for IRC [1]	All patients censored for Investigator but events for IRC [1]	1 (6.3%)	2 (8%)	3 (7.3%)
Events	All events	7 (30.4%)	20 (44.4%)	27 (39.7%)
	Death without documented progression [2]	2 (28.6%)	3 (15%)	5 (18.5%)
	Documented progression [2]	5 (71.4%)	17 (85%)	22 (81.5%)

Abbreviations: SOC = Standard of Care.
[1] Total number of censored patients with PFS<7 weeks assessed by Investigator is used as denominator for the c alculation of the percentages for each arm.
[2] Total number of patients experienced an event with PFS<7 weeks assessed by Investigator is used as denomina tor for the calculation of the percentages for each arm.
Data cut-off: 06 September 2021.
Source: EMERALD EMA Request, Table 13.2.1, Annex A.

Table 56 Frequency table for PFS < 7 weeks, in ESR1-mut patients assessed by investigator

Intent-to-Treat Population (N = 478)				
Description	**Description**	**Elacestrant (N = 14)**	**SOC (N = 21)**	**Overall (N = 35)**
Censored	All censored	9 (64.3%)	13 (61.9%)	22 (62.9%)
	Censored progression or death after taking new anti-cancer therapies	3 (33.3%)	3 (23.1%)	6 (27.3%)
	No documented progression and no death (with a post-baseline tumor assessment)	2 (22.2%)	0 (0%)	2 (9.1%)
	No post-baseline assessments and no death	4 (44.4%)	10 (76.9%)	14 (63.6%)
N patients censored for Investigator but events for IRC [1]	All patients censored for Investigator but events for IRC [1]	0 (0.0%)	2 (15.4%)	2 (9.1%)
Events	All events	5 (35.7%)	8 (38.1%)	13 (37.1%)
	Death without documented progression [2]	2 (40%)	0 (0%)	2 (15.4%)
	Documented progression [2]	3 (60%)	8 (100%)	11 (84.6%)

Abbreviations: SOC = Standard of Care, ESR1-mut = ESR1 mutation.
[1] Total number of censored patients with PFS <7 weeks assessed by Investigator is used as denominator for the c alculation of the percentages for each arm.
[2] Total number of patients experienced an event with PFS <7 weeks assessed by Investigator is used as denomin ator for the calculation of the percentages for each arm.
Data cut-off: 06 September 2021.
Source: EMERALD EMA Request, Table 13.2.2, Annex A.

In order to investigate the impact of the discordance between the IRC and investigator assessments of PFS, the applicant performed sensitivity analyses in which both investigator-assessed and blinded ICR-assessed progressions are counted as events for all patients (Table 57) and *ESR1*-mut patients (Table 58).

Table 57 Progression-free survival for elacestrant vs standard of care in all patients, sensitivity analysis (intent-to-treat population)

Description	Elacestrant N = 239	SOC N = 239
Events, n (%)	204 (85.4)	199 (83.3)
Death without documented progression	5 (2.1)	6 (2.5)
Documented progression	199 (83.3)	193 (80.8)
Censored subjects, n (%)	35 (14.6)	40 (16.7)
Censored progression or death after missing $\geqslant$ 2 consecutive post-baseline tumor assessments	0 (0)	1 (0.4)
Censored progression or death after taking new anti-cancer therapies	4 (1.7)	8 (3.3)
Lost to follow-up or withdrew consent before documented progression or death	2 (0.8)	1 (0.4)
No baseline measurable or evaluable lesion	1 (0.4)	0 (0)
No documented progression and no death (with a post-baseline tumor assessment)	22 (9.2)	15 (6.3)
No post-baseline assessments and no death	6 (2.5)	15 (6.3)
Median PFS (months) [2]	1.94	1.87
95% CI for median progression-free survival [2]	1.87 - 2.14	1.84 - 1.91
Q1 (95% CI)	1.84 (1.81 - 1.87)	1.74 (1.71 - 1.81)
Q3 (95% CI)	5.32 (3.68 - 5.72)	3.71 (3.52 - 5.39)
Min, Max	0.03+, 23.95+	0.03+, 16.53+
PFS rate at 3 months (95% CI) [2]	39.16 (32.76 - 45.57)	33.30 (26.93 - 39.68)
PFS rate at 6 months (95% CI) [2]	19.13 (13.94 - 24.33)	13.12 (8.43 - 17.81)
PFS rate at 12 months (95% CI) [2]	10.59 (6.40 - 14.78)	3.77 (0.97 - 6.56)
PFS rate at 18 months (95% CI) [2]	6.40 (2.70 - 10.10)	. (. - .)
Hazard ratio [3]	0.774	
95% CI for Hazard ratio [3]	0.633 - 0.946	
2-sided p-value [4]	0.0099	

Abbreviations: CI = confidence interval; IRC = Imaging Review Committee; max = maximum; min = minimum; PFS =progression-free survival; Q1 = First Quartile; Q3 = Third Quartile; SOC = standard of care.
[1] PFS sensitivity analysis by IRC where patients who were considered events per INV and therefore censored by I RC are considered events.
[2] Calculated using Kaplan-Meier technique. CI for 25th, 50th (median) and 75th percentiles of PFS are derived based on the Brookmeyer-Crowley method using a linear transformation.
[3] The analysis was performed using a stratified Cox Proportional Hazards model with ties = Efron and the stratific ation factors: ESR1-mutational status, prior treatment with fulvestrant (yes vs no) and presence of visceral metastases (yes vs. no); the CI calculated using a profile likelihood approach.
[4] The p-value was generated by using a two-sided stratified log-rank test.
Data cut-off: 06 September 2021.
Source: EMERALD EMA Request, Table 17.1, Annex A.

Table 58 Progression-free survival for elacestrant vs standard of care in ESR-1-mut patients, sensitivity analysis (intent-to-treat population)

Description	Elacestrant N = 115	SOC N = 113
Events, n (%)	92 (80)	97 (85.8)
Death without documented progression	3 (2.6)	1 (0.9)
Documented progression	89 (77.4)	96 (85)
Censored subjects, n (%)	23 (20)	16 (14.2)
Censored progression or death after taking new anti-cancer therapies	2 (1.7)	3 (2.7)
No documented progression and no death (with a post-baseline tumor assessment)	17 (14.8)	5 (4.4)
No post-baseline assessments and no death	4 (3.5)	8 (7.1)
Median PFS (months) [2]	2.00	1.87
95% CI for median progression-free survival [2]	1.91 - 3.65	1.84 - 1.91
Q1 (95% CI)	1.84 (1.77 - 1.87)	1.74 (1.68 - 1.81)
Q3 (95% CI)	5.55 (3.78 - 10.18)	3.75 (2.14 - 5.42)
Min, Max	0.03+, 23.95+	0.03+, 13.6+
PFS rate at 3 months (95% CI) [2]	43.13 (33.66 - 52.59)	33.86 (24.63 - 43.10)
PFS rate at 6 months (95% CI) [2]	24.92 (16.63 - 33.20)	12.06 (5.54 - 18.58)
PFS rate at 12 months (95% CI) [2]	13.27 (6.54 - 20.01)	2.74 (0.00 - 6.29)
PFS rate at 18 months (95% CI) [2]	10.56 (4.21 - 16.91)	0.00 (. - .)
Hazard ratio [3]	0.643	
95% CI for Hazard ratio [3]	0.479 - 0.863	
2-sided p-value [4]	0.0034	

Abbreviations: CI = confidence interval; ESRI-mut = ESRI mutation; PFS = progression-free survival; Q1 = first quartile; Q3 = third quartile; SOC = standard of care.
[1] PFS sensitivity analysis by IRC where patients who were considered events per INV and therefore censored by IRC are considered events.
[2] Calculated using Kaplan-Meier technique. CI for 25th, 50th (median) and 75th percentiles of PFS are derived based on the Brookmeyer-Crowley method using a linear transformation.
[3] The analysis was performed using a stratified Cox Proportional Hazards model with ties= Efron and the strat ification factors: prior treatment with fulvestrant (yes vs no) and presence of visceral metastases (yes vs no); the CI calculated using a profile likelihood approach.
[4] The p-value was generated by using a two-sided stratified log-rank test.
Data cut-off: 06 September 2021.
Source: EMERALD EMA Request, Table 17.2, Annex A.

Sensitivity analysis of the primary endpoint

Table 59: PFS sensitivity analyses

	All subjects		*ESR1*-mut subjects	
	Elacestrant	**SOC**	**Elacestrant**	**SOC**
Actual PFS event analysis				
N	239	239	115	113
HR (95% CI)	0.693 (0.550-0.874)		0.542 (0.385-0.759)	
p-value	0.0014		0.0004	
Median PFS (months)	2.79	1.91	3.78	1.87
95% CI	1.94-3.78	1.87-2.10	2.20-7.39	1.87-3.29
PFS backdating analysis				

	All subjects		*ESR1*-mut subjects	
	Elacestrant	**SOC**	**Elacestrant**	**SOC**
N	239	239	115	113
HR (95% CI)	0.693 (0.550-0.874)		0.542 (0.385-0.759)	
p-value	0.0014		0.0004	
Median PFS (months)	2.79	1.91	3.78	1.87
95% CI	1.94-3.78	1.87-2.10	2.20-7.39	1.87-3.29
Unstratified analysis				
N	239	239	115	113
HR (95% CI)	0.664 (0.528-0.835)		0.531 (0.378-0.743)	
p-value	0.0004		0.0002	
Median PFS (months)	2.79	1.91	3.78	1.87
95% CI	1.94-3.78	1.87-2.10	2.17-7.26	1.87-2.14
PP analysis				
N	234	230	115	106
HR (95% CI)	0.719 (0.569-0.907)		0.543 (0.385-0.764)	
p-value	0.569-0.9070040		0.385-0.7640005	
Median PFS (months)	2.33	1.91	3.78	1.87
95% CI	1.94-3.75	1.87-2.10	2.17-7.26	1.87-2.14

Source: Study 308, Table 14.2.1.2.1; Table 14.2.1.2.2; Table 14.2.1.3.1.1; Table 14.2.1.3.2; Table 14.2.1.4.1; Table 14.2.1.4.2; Table 14.2.1.6.2; Table 14.2.1.6.1

The results for the three additional post hoc analyses were:

- **Interval censored analysis**: In all subjects, the median PFS was 3.15 months for elacestrant and 1.31 months for SOC and the HR was 0.695 (95% CI: 0.551-0.876). In *ESR1*-mut subjects, the median PFS was 3.75 months and 0.49 months for the elacestrant and SOC groups, respectively and the HR was 0.519 (95% CI: 0.368-0.731).
- **Analysis without censoring for new systemic anticancer therapies**: In all subjects, the median PFS was 2.79 months for elacestrant and 1.94 months for SOC and the HR was 0.710 (95% CI: 0.565-0.891). In *ESR1*-mut subjects, the median PFS was 3.78 months and 1.87 months for the elacestrant and SOC groups, respectively and the HR was 0.545 (95% CI: 0.389-0761).
- **Analysis with PFS events dated at the next planned visit in case of unscheduled assessment**: In all subjects, the median PFS was 3.55 months for elacestrant and 1.91 months for SOC and the HR was 0.697 (95% CI: 0.552-0.879). In *ESR1*-mut subjects, the median PFS was 3.78 months and 1.87 months for the elacestrant and SOC groups, respectively and the HR was 0.538 (95% CI: 0.380-0.756).

Upon CHMP request, the applicant provided additional analyses to determine the robustness of the PFS results concerning the PFS HR stability over time, start of new anticancer treatment, and early censoring.

PFS HR stability

Confirmation of HR stability could be done retrospectively by calculating HR at different cut-off dates. During the conduct of the study, pooled blind data were periodically downloaded and reviewed in order

to monitor the event accrual rates and to project the time necessary to collect the required number of events (Table 60). Analyses in unblinded fashion were performed only recently in order to respond to to provide the PFS at different cut-off dates.

Table 60: Cut-off dates and PFS hazard ratio for ITT patients and ES1-mut patients

Cut-off date	ITT			ESR1-mut		
	SOC Events*	ELA Events*	HR	SOC Events*	ELA Events*	HR
28 February 2021	141	117	0.614	67	50	0.513
22 April 2021	151	129	0.650	73	55	0.550
24 May 2021	149	130	0.659	73	55	0.549
09 June 2021	150	132	0.669	73	55	0.537
19 July 2021	153	139	0.678	76	57	0.516

Abbreviations: ELA = elacestrant; ESRI-mut = ESR1 mutation; HR = hazard ratio; ITT = intent-to-treat; SOC = standard of care.
*Number of events for the interim database cut-off were not adjusted as per protocol censored rules.

Sensitivity analysis for start of new anticancer therapy

A total of 7 patients had a scan after the start of new therapy. Sensitivity analyses, where the start of new therapy is reported as events, are presented in Table 61 for all patients and Table 62 for *ESR1*-mut patients as assessed by the IRC.

Table 61: Progression-free survival for elacestrant vs standard of care in all patients as assessed by blind Imaging Review Committee (IRC) (intent-to-treat population) sensitivity analysis on new anti-cancer treatment

	Elacestrant (N = 239)	SOC (N = 239)
Events, n (%)	150 (62.8)	165 (69.0)
Death without documented progression	5 (2.1)	6 (2.5)
Documented progression	139 (58.2)	150 (62.8)
New cancer therapy	6 (2.5)	9 (3.8)
Censored subjects, n (%)	89 (37.2)	74 (31)
Censored progression or death after missing $\geqslant$ 2 consecutive post-baseline tumor assessments [1]	9 (3.8)	8 (3.3)
Lost to follow-up or withdrew consent before documented progression or death	4 (1.7)	4 (1.7)
No baseline measurable or evaluable lesion	1 (0.4)	1 (0.4)
No documented progression and no death (with a post-baseline tumor assessment)	69 (28.9)	46 (19.2)
No post-baseline assessments and no death	6 (2.5)	15 (6.3)
Median PFS (months) [2]	2.33	1.87
95% CI for median progression-free survival [2]	1.94 - 3.68	1.87 - 2.07
Q1 (95% CI)	1.87 (1.84 - 1.87)	1.77 (1.74 - 1.84)
Q3 (95% CI)	10.18 (7.26 - 15.34)	4.76 (3.71 - 7.16)
Min, Max	0.03+, 23.95+	0.03+, 16.53+
PFS rate at 3 months (95% CI) [2]	48.10 (41.29 - 54.92)	37.87 (31.04 - 44.69)
PFS rate at 6 months (95% CI) [2]	33.18 (26.20 - 40.17)	19.20 (13.19 - 25.21)
PFS rate at 12 months (95% CI) [2]	21.58 (14.71 - 28.45)	8.87 (3.77 - 13.98)
PFS rate at 18 months (95% CI) [2]	16.26 (8.70 - 23.82)	-
Hazard ratio [3]	0.687	-
95% CI for Hazard ratio [3]	0.547 - 0.861	-
2-sided p-value [4]	0.0008	-

+: Censored
Abbreviations: CI = confidence interval; IRC = Imaging Review Committee; max = maximum; min = minimum; PFS =progression-free survival; Q1 = First Quartile; Q3 = Third Quartile; SOC = standard of care.

Progression is determined according to assessment by blinded IRC. PFS is defined as the time from the date of randomization until the date of objective disease progression or death (by any cause in the absence of progression).For subjects without objective disease progression or death, PFS will be censored according to SAP Section 4.7.1.1.
[1] Date of last tumor assessment before missed assessments or date of randomization, whichever is later.
[2] Calculated using Kaplan-Meier technique. CI for 25th, 50th (median) and 75th percentiles of PFS are derived based on the Brookmeyer-Crowley method using a linear transformation.
[3] The analysis was performed using a stratified Cox Proportional Hazards model with ties= Efron and the stratification factors:ESR1-mutational status (ESR1-mut vs ESR1-mut-nd), prior treatment with fulvestrant (yes vs no) and presence of visceralmetastases (yes vs no); the CI calculated using a profile likelihood approach.
[4] The p-value was generated by using a two-sided stratified log-rank test.
Note:. For patients that started a new anticancer therapy prior to death or a disease progression, the start of new t herapy is considered as an event.
Data cut-off: 06 September 2021.
Source: EMERALD EMA Request, Table 4.1.2, Annex A.

Table 62: Progression-free survival for elacestrant vs SOC in ESR1-mut patients as assessed by blinded Imaging Review Committee (IRC) (intent-to-treat population) sensitivity analysis on new anti-cancer treatment

	Elacestrant (N = 115)	SOC (N = 113)
Events, n (%)	65 (56.5)	82 (72.6)
Death without documented progression	3 (2.6)	1 (0.9)
Documented progression	59 (51.3)	77 (68.1)
New cancer therapy	3 (2.6)	4 (3.5)
Censored subjects, n (%)	50 (43.5)	31 (27.4)
Censored progression or death after missing $\geqslant$ 2 consecutive post-baseline tumor assessments [1]	5 (4.3)	3 (2.7)
Lost to follow-up or withdrew consent before documented progression or death	2 (1.7)	1 (0.9)
No documented progression and no death (with a post-baseline tumor assessment)	39 (33.9)	19 (16.8)
No post-baseline assessments and no death	4 (3.5)	8 (7.1)
Median PFS (months) [2]	3.75	1.87
95% CI for median progression-free survival [2]	2.17 - 5.55	1.87 - 2.10
Q1 (95% CI)	1.87 (1.84 - 1.94)	1.77 (1.68 - 1.84)
Q3 (95% CI)	12.62 (7.79 - NC)	3.94 (3.68 - 7.16)
Min, Max	0.03+, 23.95+	0.03+, 13.14+
PFS rate at 3 months (95% CI) [2]	53.75 (43.69 - 63.80)	38.39 (28.49 - 48.29)
PFS rate at 6 months (95% CI) [2]	39.18 (28.76 - 49.59)	17.82 (9.64 - 26.00)
PFS rate at 12 months (95% CI) [2]	25.72 (15.47 - 35.97)	7.62 (1.14 - 14.11)
PFS rate at 18 months (95% CI) [2]	23.38 (13.09 - 33.68)	-
Hazard ratio [3]	0.545	-
95% CI for Hazard ratio [3]	0.389 - 0.760	-
2-sided p-value [4]	0.0003	-

+: Censored
Abbreviations: CI = confidence interval; IRC = Imaging Review Committee; max = maximum; min = minimum; PFS =progression-free survival; Q1 = First Quartile; Q3 = Third Quartile; SOC = standard of care.
Progression is determined according to assessment by blinded IRC. PFS is defined as the time from the date of randomization until the date of objective disease progression or death (by any cause in the absence of progression). For subjects without objective disease progression or death, PFS will be censored according to SAP Section 4.7.1.1.
[1] Date of last tumor assessment before missed assessments or date of randomization, whichever is later.
[2] Calculated using Kaplan-Meier technique. CI for 25th, 50th (median) and 75th percentiles of PFS are derived based on the Brookmeyer-Crowley method using a linear transformation.
[3] The analysis was performed using a stratified Cox Proportional Hazards model with ties = Efron and the stratification factors: prior treatment with fulvestrant (yes vs no) and presence of visceral metastases (yes vs no); the CI calculated using a profile likelihood approach.
[4] The p-value was generated by using a two-sided stratified log-rank test.
Note: For patients that started a new anticancer therapy prior to death or a disease progression, the start of new th erapy is considered as an event.
Data cut-off: 06 September 2021.
Source: EMERALD EMA Request, Table 4.1.1, Annex A.

Early censoring

During the first 2 months after randomization, the KM curves show 92 (31.9%) censored subjects. The numbers are relatively balanced among the two treatment arms with 40 (30.1%) subjects in the elacestrant arm and 52 (33.5%) subjects in the SOC arm. Later censoring is higher in the elacestrant arm (55 (52%) subjects) vs the SOC arm (31 (37%) subjects) reflecting the fact that patients in the elacestrant arm stay longer in treatment with no progression. Reasons for IRC-censoring during the first 2 months after randomization are reported in the following tables.

Table 63 Frequency table for PFS ≤ 2 months, in all subjects assessed by blinded Imaging Review Committee (IRC)

Description	Description	Elacestrant N = 133	SOC N = 155	Overall N = 288
All censored	All censored, n(%)	40 (30.1)	52 (33.5)	92 (31.9)
	Censored progression or death after missing ≥ 2 consecutive post-baseline tumor assessments [1]	5 (12.5)	5 (9.6)	10 (10.9)
	Censored progression or death after taking new anti-cancer therapies [1]	6 (15)	8 (15.4)	14 (15.2)
	Lost to follow-up or withdrew consent before documented progression or death [1]	2 (5)	3 (5.8)	5 (5.4)
	No baseline measurable or evaluable lesion [1]	1 (2.5)	1 (1.9)	2 (2.2)
	No documented progression and no death (with a post-baseline tumor assessment) [1]	20 (50)	20 (38.5)	40 (43.5)
	No post-baseline assessments and no death [1]	6 (15)	15 (28.8)	21 (22.8)

[1] Total number of censored patients with PFS ≤ 2 assessed by IRC is used as denominator for the calculation of the percentages for each arm
Source: EMERALD EMA Request, Table 25, Annex A

The applicant performed a tipping point analysis following two different approaches:

- Approach 1:

All patients censored within the first 2 months were considered as events. Then +1 day was added incrementally to the date of the event for those patients in both groups at each analysis run. A hazard ratio of 1 was never reached, even after adding 10000 days (HR = 0.79 for ALL patients, and HR = 0.577 for ESR1-mut). It was concluded that even such an unlikely deviation would still keep the results statistically significant in favor or elacestrant.

- Approach 2:

To perform the tipping point analysis, censored patients were turned into events for the elacestrant arm only (representing the worst-case scenario), sorting the patients by time to censoring (ascending order).

When all the first 40 censored patients were transformed into the event, the HR still favours the ELA (HR of 0.923 in all subjects and 0.808 in ESR1-mut patients). The process then continued by transforming into events one by one all the remaining patients censored with a PFS time greater than 2 months.

The tipping point was found to be between 55 and 60 for the all-patient population, while in the ESR1-mut population HR never reaches 1.0 even when all the censored patients in the elacestrant arm are turned into events (maximum HR equal to 0.929).

Subgroup analyses for OS

Table 64. Subgroup analysis of overall survival for elacestrant vs SOC, in ESR1-mut subjects at the time of final OS analysis (intent-to-treat population)

	Elacestrant		SOC		
	No. of Events/ No. of Subjects	**Median (95% CI) [1]**	**No. of Events/ No. of Subjects**	**Median (95% CI) [1]**	**HR (95% CI) [2]**
All Subjects	**61/115**	**24.18 (20.53, 28.71)**	**60/113**	**23.49 (15.64, 29.90)**	**0.891 (0.624, 1.275)**
Prior Treatment with Fulvestrant					
Yes	16/27	22.64 (18.46, 31.87)	17/28	15.64 (10.41, 32.72)	0.797 (0.397, 1.596)
No	45/88	25.30 (20.40, 31.93)	43/85	26.25 (16.26, 32.62)	0.940 (0.617, 1.436)
Presence of Visceral Metastasis					
Yes	41/79	25.95 (20.40, 31.87)	45/80	21.32 (14.36, 28.88)	0.839 (0.546, 1.288)
No	20/36	22.57 (18.60, NC)	15/33	24.28 (15.87, NC)	1.125 (0.578, 2.238)
Age Group (years)					
<65	36/62	22.57 (19.84, 26.25)	30/62	24.28 (16.95, 28.88)	1.124 (0.693, 1.837)
≥65	25/53	31.87 (19.68, NC)	30/51	15.05 (12.68, 32.72)	0.712 (0.412, 1.220)
<75	54/98	22.64 (20.40, 27.73)	47/96	26.25 (17.45, 32.72)	1.048 (0.709, 1.554)
≥75	7/17	31.87 (16.95, NC)	13/17	11.73 (4.96, 15.64)	0.390 (0.143, 0.982)
Race					
Caucasian	41/84	25.82 (20.67, 32.99)	45/80	17.74 (14.29, 28.88)	0.690 (0.450, 1.055)
Asian	2/5	31.93 (8.84, NC)	3/8	NC (12.09, NC)	1.289 (0.169, 7.799)
Other [3]	5/5	18.96 (0.85, NC)	2/4	27.66 (3.58, NC)	2.264 (0.474, 16.156)
Region					
Europe	35/63	24.18 (18.60, 31.87)	29/50	19.78 (14.00, 29.90)	0.813 (0.497, 1.342)
North America	18/33	20.53 (18.96, 27.73)	21/42	23.49 (14.29, NC)	1.063 (0.560, 2.000)
Asia	5/10	31.93 (25.30, NC)	8/16	24.28 (14.36, NC)	0.829 (0.250, 2.494)
Baseline ECOG Performance Status					
0	34/67	22.64 (19.84, 32.99)	30/62	28.52 (17.74, NC)	1.048 (0.640, 1.723)
1	27/48	25.30 (17.28, 31.87)	30/51	16.26 (12.39, 26.25)	0.744 (0.439, 1.254)
Measurable Disease at Baseline					
Yes	51/92	22.57 (19.84, 28.71)	49/92	26.25 (14.82, 29.90)	1.028 (0.692, 1.531)
No	10/23	27.73 (19.68, NC)	11/21	17.74 (14.29, NC)	0.546 (0.226, 1.302)
Number of prior lines of endocrine therapy in the adv/met setting					
1	38/73	24.18 (18.27, 31.93)	29/69	29.90 (21.32, NC)	1.341 (0.824, 2.210)
2	23/42	26.25 (19.81, 32.99)	31/44	15.64 (12.16, 19.78)	0.495 (0.284, 0.852)
Number of lines of chemotherapy in the adv/met setting					

	Elacestrant		SOC		
	No. of Events/ No. of Subjects	**Median (95% CI) [1]**	**No. of Events/ No. of Subjects**	**Median (95% CI) [1]**	**HR (95% CI) [2]**
0	44/89	26.25 (21.98, 32.99)	38/81	28.52 (18.66, 32.62)	0.927 (0.601, 1.438)
1	17/26	18.27 (13.93, 22.64)	22/32	14.82 (11.96, 17.74)	0.954 (0.496, 1.806)

SOC = Standard of Care, ESR1-mut = ESR1 mutation, CI = Confidence Interval, HR = Hazard Ratio, adv/met = advanced/metastatic.
[1] Calculated using Kaplan-Meier technique. CI for median of OS are derived based on the Brookmeyer-Crowley method using a linear transformation.
[2] HR is calculated using an unstratified Cox Proportional Hazards model with ties= Efron. The CI is calculated using a profile likelihood approach.
[3] Includes subjects with multiple races.
Database cut-off date: 02SEP2022, Database extraction date: 13OCT2022
Source: Emerald-308_OS_Table 14.2.2.3.1

The planned sensitivity analysis examining censoring patterns for OS showed results that were not significantly different for the elacestrant arm when compared to the SOC arm in both all patients and patient with *ESR1* mutation. In terms of Kaplan-Meier curves the differences were not indicative for any systematic difference in timing of censoring that would be considered of clinical relevance for the *ESR1*-mut population which is the focus of the indication.

Post hoc analysis: Overall survival modelling

To understand the probability of success for the OS endpoint when the final analysis is conducted at approximately 239 deaths in all subjects, 2 post hoc approaches were used to estimate the expected power for this final OS analysis. The first approach was a conditional power estimation to calculate the expected power based on the number of deaths observed at the DCO date (06 September 2021) (Gao et al*, Journal of Biopharmaceutical Statistics*, 2008). This approach estimated the power to be 65.6% for all subjects and 90.4% for *ESR1*-mut subjects. The second approach to estimating power was based on modelling and conditional simulations. The hazard rate for each treatment was estimated based on the OS data observed at the time of the OS interim analysis (DCO: 06 September 2021). An exponential distribution was assumed, and data were simulated for the future course of the study (taking into account the time that existing subjects had already been in the study) until 239 deaths were accumulated. The simulations were repeated 10,000 times and the probability of success was reported as the proportion of null hypotheses rejected at the final OS analysis among the 10,000 simulated runs. These simulations estimated a probability of success of 68.81% for all subjects and 90.78% for *ESR1*-mut subjects.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 65 Summary of efficacy for trial RAD1901-308

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, multicentre trial	
Study identifier	RAD1901-308, EudraCT number: 2018-002990-24, EMERALD Study
Design	Phase 3 open-label, multicentre, randomized, active-controlled, event-driven clinical study with evaluation of efficacy and safety of elacestrant in

	comparison to SOC endocrine monotherapy including the options of fulvestrant or aromatase inhibitor (AI).		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		2019 to 2021 (ongoing for survival follow-up) not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Elacestrant		Elacestrant 100 or 400 mg tablets, until progression/unacceptable toxicity, number randomised 239
	Standard of care (SOC)		Fulvestrant or aromatase inhibitor (AI; anastrozole, letrozole, or exemestane), until progression/unacceptable toxicity, number randomised 239
Endpoints and definitions	Primary endpoint	Progression-free survival (PFS)	PFS by independent review committee (IRC): • in all patients • in patients with *ESR1*-mutations (*ESR1*-mut)
	Key Secondary endpoint	Overall survival (OS)	OS: • in all patients • in patients with *ESR1*-mut
	Secondary endpoint	PFS in *ESR1*-mut-nd	PFS by IRC in patients with no detected *ESR1* mutation
	Secondary endpoint	OS in *ESR1*-mut-nd	OS in patients with no detected *ESR1* mutation
	Secondary endpoint	Local investigator-assessed PFS	PFS by investigator
	Secondary endpoint	Objective response rate (ORR)	ORR by IRC: • in all patients • in patients with *ESR1*-mut
Database lock	06September 2021 for PFS analysis 02September 2022 for final OS analysis in overall and *ESR1*-mut population		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat Median duration of follow-up is not provided. The median duration of exposure to elacestrant was 2.8 months (range: 0.4 to 24.8). Average treatment duration 144 days for elacestrant, 123 days for fulvestrant, 97 days for AI		
Descriptive statistics and estimate variability	Treatment group	**Elacestrant**	**SOC**
	Number of subjects All patients *ESR1*-mut ESR1-mut-nd	 239 115 124	 239 113 126
	PFS by IRC (median months) **All patients** ***ESR1*-mut**	 2.79 3.78	 1.91 1.87
	95% CI All patients *ESR1*-mut	 1.94-3.78 2.17-7.26	 1.87-2.10 1.87-2.14
	OS (median months) **All patients** ***ESR1*-mut**	 24.61 24.18	 22.57 23.49

	95% CI All patients *ESR1*-mut	 20.67-29.47 20.53-28.71	 18.14-28.88 15.64-29.90
	PFS in *ESR1*-mut-nd (median months)	1.94	1.97
	95% CI	1.87-3.55	1.87-2.20
	OS in *ESR1*-mut-nd (median months)	NE	NE
	95% CI	18.83-NE	15.80-NE
	PFS per investigator (median months) **All patients** ***ESR1*-mut** 95% CI All patients *ESR1*-mut	 2.17 3.65 1.94-3.58 2.10-5.36	 2.00 2.07 1.87-2.14 1.87-3.48
	ORR by IRC (%) **All patients** ***ESR1*-mut** 95% CI All patients *ESR1*-mut	 4.5 7.1 1.95-8.62 2.63-14.73	 4.4 4.7 1.92-8.48 1.28-11.48
Effect estimate per comparison	Primary endpoint: **PFS by IRC** **All patients** ***ESR1*-mut**	Comparison groups Hazard ratio 95% CI P-value stratified log rank test 	Elacestrant versus SOC 0.697 0.546 0.552-0.880 0.387-0.768 0.0018 0.0005
	Key secondary endpoint: **OS** **All patients** ***ESR1*-mut**	Comparison groups Hazard ratio 95% CI P-value stratified log rank test 	Elacestrant versus SOC 0.912 0.903 0.708-1.175 0.629-1.298 0.48 0.58
	Secondary endpoint: **PFS in *ESR1*-mut-nd**	Comparison groups Hazard ratio 95% CI P-value stratified log rank test	Elacestrant versus SOC 0.863 0.628-1.186 0.3082
	Secondary endpoint: **OS in *ESR1*-mut-nd**	Comparison groups Hazard ratio 95% CI P-value stratified log rank test	Elacestrant versus SOC 0.894 0.577-1.386 0.6141
	Secondary endpoint: **PFS per investigator (median months)** **All patients** ***ESR1*-mut**	 Comparison groups Hazard ratio 95% CI P-value stratified log rank test 	 Elacestrant versus SOC 0.769 0.647 0.625-0.945 0.477-0.876 0.0097 0.0049
	Secondary endpoint: **ORR by IRC** **All patients**	Comparison groups P-value stratified CMH test	Elacestrant versus SOC 0.959

	***ESR1*-mut**		0.499
Notes	A post hoc exploratory subgroup PFS analysis by IRC was performed based on the stratification factor **prior fulvestrant**. HRs for patients with and without prior fulvestrant treatment were 0.673 (95% CI: 0.438-1.029) and 0.668 (95% CI: 0.508-0.877), respectively in the overall population. In the *ESR1*-mut population, HRs for patients with and without prior fulvestrant treatment were 0.621 (95% CI: 0.297-1.257) and 0.513 (95% CI: 0.348- to 0.752), respectively. Post hoc analyses were performed to compare elacestrant to fulvestrant and elacestrant to AI for PFS by IRC: • **Elacestrant vs fulvestrant**: Overall, 165 out of 239 patients (69%) received fulvestrant as the SOC treatment. HR in the overall population was 0.684 (95% CI: 0.521-0.897). HR for *ESR1*-mut patients was 0.504 (95% CI: 0.341-0.741). • **Elacestrant vs AI**: Overall, 73 out of 239 patients (31%) received fulvestrant as the SOC treatment. HR in the overall population was 0.779 (95% CI: 0.520-1.172). HR for *ESR1*-mut patients was HR was 0.659 (95% CI: 0.320-1.329).		

2.6.5.3. Clinical studies in special populations

Table 66 Age distribution for older subjects (safety population)

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials (N = 467)	127 (27.2%)	84 (18%)	2 (0.4%)
Controlled Trial - elacestrant Arm (N = 237)	63 (26.6%)	38 (16%)	2 (0.8%)
Non Controlled Trials (elacestrant) (N = 64)	19 (29.7%)	5 (7.8%)	0 (0%)

Overall Safety Population includes 531 patients: 467 from Controlled Trial (RAD1901-308) and 64 from Non-Controlled Trials (RAD1901-005 and RAD1901-006).
Data cut-off: 08 July 2022.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Scientific rationale for ESR1 *mutation testing*

Mechanism of action: elacestrant binds to the ligand binding domain of ERα (the protein coded by the ESR1 gene) with high affinity. The binding affinity data for the mutant variants such as Y537S and D538G are not available. Elacestrant also binds estrogen receptor-beta (ERβ) but with lower (high nanomolar) affinity. Elacestrant inhibited proliferation of MCF-7 breast cancer cells featuring wt *ESR1* or mut *ESR1* (Y537S and D538G) with IC_{50} values in the lower nanomolar range. Oral administration of elacestrant produced dose-dependent tumour growth inhibition (TGI) of established tumours in an estrogen-responsive MCF-7 human breast carcinoma CDX mouse model and in PDX mouse models, using breast cancer cells insensitive to fulvestrant and CDK4/6 inhibitors or cells harbouring mutations in *ESR1*.

Biomarker definition: "Any ESR1 mutation between codons 310 and 547" was utilised to define a patient to be 'ESR1 mutation positive' ('ESR1-mut'). This means the definition covers any mutations in the ESR1 ligand domain and therefore follows the rationale that any ESR1 mutation in the ligand domain leads to resistance to endocrine therapy (Toy et al., Nat. Genetics 2013, Brett et al. Breast Cancer Res. 2021).

While certain specific mutations (e.g., D538G, Y537S, Y537N) are most common, ESR1 mutations can be highly diverse. This is supported by data from study RAD1901-308 (EMERALD), being the pivotal study in this procedure (n=478 patients). All together in this study 44 different distinct mutations were detected. 64% (28/44) of these mutations were detected with the frequency of one (n=1), and another 11% (5/44) were not encountered in the literature before.

In summary, the following ESR1 mutations were detected in study RAD1901-308 (regardless of number of ESR1-mutations detected in one patient):

- Detected ≥10 times (in the order of frequency detected): D538G, Y537S, Y537N, E380Q, L536H, Y537C
- Detected ≤10 times (in the order of frequency detected): L536P, L536R, S463P, H524L, Y537D, M543L, F404L, M421L, H356D, D351H, D351N, E397D, E542D, E542Q, H356Y, L370F, L536Q, L539V, L539H, L541P, M342L, M543T, P535S, R503Q, S329A, V392I, V534G, E380K, F404I, F404V, L379I, L536V, M343I, M357I, R503W, V533M, V534L, Y537H

As to a subgroup analysis from Study RAD1901-308, observed median PFS is similar in patients with rare mutations (frequency n=1) compared to patients positive for any eligible ESR1 mutation. In addition, median PFS from subgroup analyses for the four most frequently detected mutations are supportive (see Table 67 below).

Table 67: Median PFS for each variant detected by Guardant360 CDx (within the proposed biomarker definition) with a frequency of 6 or more in either treatment arm regardless of the number of ESR1 mutations detected in that patient

	Elacestrant			**Standard of Care**		
Mutation	**# patients**	**# events**	**Median PFS***	**# patients**	**# events**	**Median PFS***
D538G	70	36	4.140	68	52	1.873
Y537S	49	25	3.647	39	25	1.873
Y537N	34	19	4.140	30	23	1.938
E380Q	15	9	3.778	15	9	2.103
L536H	7	5	4.994	9	8	3.745
Y537C	7	4	7.261	7	4	1.922

Abbreviations: CDx = companion diagnostic; PFS = progression-free survival.
* Median PFS is calculated by fitting a Kaplan-Meier curve for each grouping.
Median PFS for each variant detected by Guardant360 CDx (within the proposed biomarker definition) and limited to only the instances when the subjects had a single mutation in ESR1 gene.

Local tests

In the pivotal study RAD1901-308 only a central test but no local tests investigating the ESR1-mutation status were performed.

Confirmation test

Guardant360 (Guardant Health, Redwood City, CA) was the only assay used to determine the ESR1 mutation status in the single pivotal study RAD1901-308 (EMERALD).

Analytical method including assay platform, specimen, pre-analytical processing requirements and read-out method

Guardant360 is a qualitative next generation sequencing-based *in vitro* diagnostic device that uses targeted high throughput hybridization-based capture technology for detection of biomarkers utilizing circulating tumour DNA (ctDNA) (i.e. it as so-called liquid biopsy) and is used to detect ESR1 mutations between codons 310 and 547.

Literature shows that ctDNA is a commonly used method to determine *ESR1* mutation status. The review of Downton et al., *Drug Design, Development and Therapy*, 2022, describes that *ESR1* mutations may be detected from tumour tissue or circulating tumour DNA with good concordance between the two specimen types.

Guardant360 CDx is a laboratory test composed of the following major processes: Whole Blood Collection and Shipping, Plasma Isolation and circulation cell-free DNA (cfDNA) Extraction, Library Preparation and Enrichment DNA Sequencing, Data Analysis and Reporting. Whole blood is collected in the provided blood collection tubes, Streck Cell-Free DNA BCTs, which stabilise cfDNA and nucleated blood cells for shipping. The blood sample is sent to a laboratory for testing. A minimum of 5 mL whole blood is required for testing. Plasma is isolated via centrifugation and cfDNA is extracted from plasma within 7 days. Extracted cfDNA, 5 to 30 ng, is then used to prepare sequencing libraries which are enriched by hybridization capture. The enriched libraries are then sequenced using next generation sequencing on the Illumina NextSeq 550 platform. Quality control measures are taken throughout sample processing and sequencing. cfDNA quantity and fragment size distribution are measured at several points during sample processing to ensure sample integrity. Additionally, a sequence variant control, containing both expected positive and negative variants (the Variant Control) are used with each batch. All the somatic quality control measures must pass for each sample result to be considered valid. Sequencing data are analyzed using a custom-developed bioinformatics pipeline. Upon completion of testing, a Guardant360 CDx results report will be generated for use by a qualified individual with appropriate clinical training.

Clinical validation strategy

To support clinical validity of Guardant360 CDx as a predictive biomarker, the treatment effect of elacestrant vs SOC for PFS in ESR1-muation positive patients was descriptively compared with the treatment effect of elacestrant in ESR1-mutation not detected patients from pivotal study RAD1901-308 (EMERALD) (see discussion on clinical efficacy).

Cut-point selection

Table 68: Guardant360 CDx BIP SNV calling cut-offs

SNV Calling Property	Metric
DNA Molecule Support	≥ 2
MAF Estimate	≥ 0.001%
Log Likelihood Ratio	≥ 0

MAF = minor allele frequency

No clinical thresholding was performed. Therefore, it remains unclear whether the threshold applied in study RAD1901-308 (EMERALD) was optimal or whether a lower or higher threshold defining patients as 'ESR1-mutant' would lead to a better benefit-risk ratio.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

2.6.5.6. Supportive study(ies)

Not applicable.

2.6.6. Discussion on clinical efficacy

In this MAA, the applicant submits the clinical study results in support of the following indication (wording amended during the evaluation):

"Orserdu monotherapy is indicated for the treatment of postmenopausal women, and men, with estrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK4/6 inhibitor."

Orserdu (elacestrant) is a tetrahydronaphthalene compound that is a selective and orally active oestrogen receptor-α (ERα) degrader and antagonist (SERD). The recommended dose is 400 mg (one film-coated tablet), once daily, with or without food.

The clinical development programme in support of the proposed indication concerns three clinical studies; two phase 1 studies (Study 005 and 106) and one phase 3 randomised control trial (RCT) (Study 308, RAD1901-308, EMERALD), the latter is considered key for the proposed indication.

Scientific advice (SA) was sought for Study 005. Based on the SA, the applicant revised the intended clinical strategy with Study 308 as main pivotal study to support the MAA.

Dose finding and dose recommendation

The recommended dose of 400 mg once daily (QD) in Study 308 was based on Study 005 and Study 106.

Within the dose escalation **Study 005**, only 7 out of the 57 enrolled patients received another dose than 400 mg QD. Although no dose-limiting toxicities were reported, the 600 mg dose (capsules only) was deemed not tolerable due primarily to gastrointestinal (GI) events (especially nausea, vomiting, and constipation) occurring at higher frequencies compared to the 400 mg dose (67%-100% vs 17%-65%). The low number of patients treated with 200 mg (n=4) and 600 mg (n=3) hampers the comparison between the different doses. It is also noted that the 400 mg tablets seem to be more tolerable than the 400 mg capsules and higher doses of the tablets might have been tolerable as well. The objective response rate (ORR) of 19.4% in 31 evaluable patients receiving the recommended phase 2 dose in Study 005 supports single-agent activity. ORR was 16.7% in 18 patients who received prior CDK4/6i and 23.1% in 13 patients who were naïve to CDK4/6i.

Results from the pharmacodynamic **Study 106** showed that both doses of 400 mg and 200 mg reduced FES uptake in tumour lesions at day 14, although less reduction was observed with the 200 mg dose (see 2.6.2.2.). The applicant provided further support for the intended dose with PopPK model simulations of 200 and 400 mg QD for a patient population with the same covariate distribution of the phase 3 study 308 population. The PopPK model showed that with 200 mg QD, only half of the patients would have resulted above the target engagement threshold, while the totality of the patients administered with 400 mg QD would have reached through concentrations above the threshold. This seems to be contradicting the observation that there was no clear relationship between PFS and elacestrant exposure, as represented by the average daily AUC (AUCav) (see 2.6.2.).

In the final exposure response analysis, the nominal steady state AUC(0-24) for the patients in Study 308 were overlaid on the logistic curves of (i) the probability of clinical benefit rate and overall response vs AUC and (ii) the probability SAE, Grade 3 AEs and AEs leading to study discontinuation vs AUC obtained in a preliminary analysis based on efficacy and safety data from the phase 1 Studies 005 and 106. The probability of experiencing any type of severe AEs increased for doses higher than 400 mg QD, while in the range of exposures observed in Study 308 study this probability did not increase markedly, remaining below 50%. The probability of clinical benefit and overall response seemed to be decreasing with a higher AUC, which is not explained.

All in all, any conclusions on the most optimal dose are still difficult to draw and it is not understood how the dose recommendation was determined to be 400 mg QD. However, it is acknowledged that the B/R assessment should be made based on the posology of 400 mg QD used in the pivotal study. However, given the limited data on the 200 mg dose (n=4), the apparent lower target engagement and no patients in the pivotal study in need of a second dose reduction (see 2.6.2. and 2.6.8.), the possibility that patients receiving 200 mg dose would be undertreated cannot be ruled out. Therefore, the recommendation for the second dose reduction was not supported (See SmPC section 4.2).

Design and conduct of clinical studies

In- and exclusion criteria- Study 308 is a phase 3, multicentre, randomised, open-label, active-controlled study comparing of elacestrant versus standard of care (SOC) therapy (fulvestrant or aromatase inhibitor (AI)) in postmenopausal women and men with ER+/HER2- metastatic breast cancer (mBC) whose disease has relapsed or progressed on at least 1 and no more than 2 prior lines of endocrine therapy (ET) for mBC. Prior ET must have included a combination with CDK4/6 inhibitor (CDK4/6i) therapy and patients must have received no more than 1 line of cytotoxic chemotherapy for mBC and must have been appropriate candidates for endocrine monotherapy. Only patients with evaluable lesions per RECIST version 1.1, i.e. measurable disease or bone only disease with evaluable lesions were included. The in- and exclusion criteria largely reflect the target population, although more fit than the to be treated population in clinical practice and presented with not rapidly progressing disease. For instance, patients with ECOG >1, presence of symptomatic metastatic visceral disease, cardiac comorbidity, and hepatic impairment were excluded.

The applicant originally proposed an indication irrespective of prior CDK4/6i status, but patients had to be previously treated with endocrine therapy in combination with CDK4/6i to be enrolled in the pivotal study. Although it is known that efficacy of fulvestrant is different in patients who progressed on a CDK4/6i compared to patients CDK4/6i naïve (Lindeman et al., Clinical Cancer Research, 2022), the impact of prior CDK4/6i therapy on the activity of elacestrant is not known based on the provided data. Although the results of Study 005 provide clinical evidence of activity of elacestrant in CDK4/6i naïve patients, it cannot be concluded that elacestrant activity among CDK4/6i-naïve patients compares favourably to its activity in patients who received prior CDK4/6i in the metastatic setting. Additional limitations to interpret the clinical data from Study 005, are the limited number of patients, the single arm study design and the response rates being higher than observed in the pivotal study, which make

it difficult to put the results into perspective. The applicant also provided PFS results for subgroups with different duration of prior CDK4/6i therapy which showed a positive correlation between the duration of prior CDK4/6i and PFS on elacestrant in Study 308, which was not observed in the control arm. All in all, the efficacy of elacestrant in patients who are CDK4/6i naïve remains uncertain with clinical data limited to only 13 patients in Study 005. Therefore, the indication was restricted to patients with prior CDK4/6i treatment, in line with the inclusion criteria of the pivotal Study 308.

***ESR1* mutation testing**: *ESR1* mutations are a known resistance mechanism to endocrine therapy. Further, the specific mutation in the *ESR1* gene appears of importance as there is mutation-specific variability in resistance patterns (Lloyd et al., *Therapeutic Advances in Medical Oncology*, 2022). Acquired drug resistance to endocrine therapy may also occur by activation of alternative growth factor and signalling pathways, such as the PI3K/AKT/mTOR pathway (Downton et al., *Drug Design, Development and Therapy*, 2022). The applicant initially planned to conduct exploratory biomarker analyses which were deleted in the statistical analysis plan (SAP) of 05 March 2021.

While the role of *ESR1* mutations in the resistance to aromatase inhibitor treatment is evident, the role of *ESR1* mutations is less clear in respect to treatment with SERDs in general or to what extent differential treatment effects can be expected for fulvestrant and elacestrant. Non-clinical studies in animal models bearing *ESR1*wt or *ESR1*mut xenografts did show a generally better efficacy of elacestrant as compared to fulvestrant in the mutant variants, but a mechanistic background remains largely unclear. *In vitro*, fulvestrant was shown to inhibit both wild-type and mutant ER more effectively than elacestrant but receptor occupancy *in vivo* may be incomplete at the concentrations achieved in patients. From the clinical point of view, the advantage claimed for elacestrant based on the non-clinical evidence cannot directly be found in the clinical evidence for *ESR1*-mut and *ESR1*-WT tumours. While certain specific ESR1 mutations (e.g., D538G, Y537S, Y537N) are most common, ESR1 mutations can be highly diverse. The scientific rationale to define patients with 'any ESR1 mutation in the ligand binding domain (i.e. any mutation between codons 310 and 547)' as ESR1 mutation positive ('ESR1-mut') – being supported by preclinical data – can be followed. The non-clinical studies provided no evidence of the improved efficacy of elacestrant in the investigated models with mut *ESR1* in comparison to wt *ESR1* models. Post-hoc defined subgroup analyses from pivotal study RAD1901-308 are supportive for this definition. However, a sound validation of this definition of ESR1 mutation positivity (i.e. biomarker positivity) is not possible due to the diversity and rarity of single ESR1 mutations within the ligand binding domain. In view of the narrowed proposed indication to ESR1 mutated patients the unclear pre-clinical and clinical selectivity to mutant ESR1 over wt-ESR1 will not be further pursued. However, pharmacodynamics of elacestrant with regard to ESR1 mutation still lack clarification.

The *in vitro* biomarker Guardant360 (Guardant Health, Redwood City, CA) was the assay used to determine the *ESR1* mutation status in the single pivotal study RAD1901-308 (EMERALD), which was used to stratify the population. Analytical validation of Guardant360 CDx with regard to accuracy, sensitivity, specificity, precision and robustness was demonstrated. Eligibility of patients for elacestrant was based on analytical detection of the mutations by Guardant360 CDx. Mutation results are provided as 'biomarker positive' or 'biomarker negative', i.e. Guardant360 CDx is a purely qualitative binary test. No clinical thresholding was performed.

Clinical validation: When using the Guardant360 CDx as basis for deciding on ESR1-mutation status, The PFS benefit of elacestrant vs SOC in the ESR1-mutation positive patient population was numerically larger than in ESR1-mutation not detected patient population supporting predictivity. This does not mean that any ESR1-mutation detected by the test is predictive, or that ESR1-mutation status is predictive independently from the chosen cut-off. The explorative analysis by mutation (see Table 67) and the analysis of pooled rare mutations do not contradict the assumption of a homogeneous effect across mutations. However, the limitations of these analyses, such as not all

mutations being represented in the study, small sample sizes and median alone not describing treatment effects comprehensively, mean that no definite conclusion on consistency of effects across mutations is possible based on the clinical data.

Cut-point selection: Eligibility of patients for elacestrant was based on analytical detection of the mutations by Guardant360 CDx. Mutation results were provided as 'biomarker positive' or 'biomarker negative', i.e. Guardant360 CDx is a purely qualitative binary test. No clinical thresholding was performed. Therefore, it remains unclear whether the threshold applied in study RAD1901-308 (EMERALD) was optimal or whether a lower or higher threshold defining patients as 'ESR1-mutant' would lead to a better benefit-risk ratio.

As the relevant *ESR1* mutations leading to oestradiol independent receptor activation are those in the ligand binding domain, it is specified in the indication that the *ESR1* mutations have to be activating.

Comparator: Fulvestrant and AI (anastrozole, letrozole, and exemestane) monotherapy are valid options according to the ESMO guideline (Gennari et al., *Annals of Oncology*, 2021) for candidates for endocrine monotherapy (per the inclusion criteria). Other therapeutic options are mainly for specific subgroups with a mutation (alpelisib, PAPR inhibitors). Tamoxifen monotherapy would have been another SOC option though. The investigator was to select 1 of the available SOC options based on the individual patient's prior treatment history and the investigator's judgment prior to randomisation. The general protocol guidance on choice of SOC, i.e. aromatase inhibitor vs fulvestrant according to prior treatments is acknowledged. It appears appropriate to change the class of substance after progression to avoid likely inefficient treatment.

Duration of treatment: Study treatment was administered until progressive disease (PD), death, unacceptable toxicity, inability to receive study treatment for >14 days or withdrawal of patient consent, which can be supported given the mechanism of action of endocrine therapies.

Efficacy endpoints: Patients were randomised 1:1 to elacestrant or SOC, stratified by *ESR1* mutational status, prior fulvestrant, and visceral metastases. The principle of randomisation and the stratification factors used are supported.

The primary endpoint is progression-free survival (PFS) by imaging review committee (IRC) using RECIST v1.1 with OS as the key secondary endpoint. Tumour assessments were performed every 8 weeks ±7 days from randomisation date. PFS is an acceptable endpoint in the proposed setting, provided mature OS data excluding a negative effect are available and the effect is homogenous across important subpopulations. Both PFS and OS were analysed in the *ESR1*-mut patients and in all patients and the primary endpoint was defined as met if the PFS was statistically significant in either one of the two populations (intent-to-treat (ITT) analysis). PFS and OS *ESR1*-mut-not detected (nd), containing both patients who have proven WT disease and patients in whom the test could not be performed, are analysed as unpowered secondary endpoints. The choice of secondary endpoints was supported.

Sample size: The sample size calculation appeared incomplete as it was performed for the *ESR1*-mut population and the assumption was based on treatment with fulvestrant only, even though the SOC also included AI and the study could also become positive if the PFS in the overall population would be significant.

Statistical methods: The difference in the primary endpoints IRC-assessed PFS between the treatment groups was analysed using a log-rank test stratified by the stratification factors, which is an acceptable method. In the primary PFS analysis, documented progression or death after missing ≥2 consecutive postbaseline tumour assessments and progression after start new anticancer therapy were not considered as PFS events. These do not follow the CHMP guideline on PFS (EMA/CHMP/27994/2008/Rev.1), as >1 missed visits are censored as is start new anti-cancer therapy. Post hoc analysis were provided to address this. Since no tumour assessments were required by

protocol after start of new anticancer therapy, these analyses are automatically hampered for assessing progression after start of new anticancer therapy. The other sensitivity analyses and concordance analysis between IRC- and investigator-assessed PFS, which were performed as planned, are agreed.

The analysis methods for the other secondary endpoints are in general agreed. It should be noted, however, that PRO results are mainly summarising outcomes with no formal statistical testing planned. Additionally, hypothesis and handling of missingness are not provided for PRO data and claims on PRO benefit will be difficult to make.

The planned subgroup analyses are supported, although the subgroups based on SOC choice, i.e. AI or fulvestrant, were not prespecified.

Study conduct: Most of the study protocol amendments that occurred after the enrolment of the first study patient are not likely to have a major influence on the efficacy outcomes. However, late changes were made in the analysis of the main efficacy endpoints PFS and OS in an open-label trial, which questioned the internal validity.

Firstly, the final PFS analysis was performed with less events than prespecified in the SAP for the final analysis. The applicant explained that the assumed efficacy based on median PFS was lower than expected and the number of censoring was higher than expected. This led to a lower number of events and it was projected that the planned number of events would not be reached within a year. The process of managing access to treatment information was documented in a blind management plan (final version dated 01-February 2021) before the data cut-off of 06 September 2021 and subsequent changes in the blind management did not included changes in who had access to what information. Although the decision for changing the analysis time point seems to have been made by persons not blinded to treatment assignment, these had no access to aggregated data. In addition, additional analyses with an updated PFS analysis and stable HR ratios over time support that the final PFS analysis provided can be regarded as a reliable alternative to the originally planned final analysis (see under Efficacy data and additional analyses).

Moreover, the timing of the interim and final OS analysis were specified in the protocol - version 5.0 dated March 2019, which was still at the very early stage of the trial and very few patients were enrolled at that time. OS was defined as a key secondary efficacy endpoint for the *ESR1*-mut and overall population. The interim analysis was planned at the time of the primary (final) PFS analysis and the final OS analysis was to be performed when 50% of the subjects had died but no specification for controlling Type 1 error at 2-sided alpha at 0.05 in the primary and secondary endpoints was initially specified. During the study, the Food and Drug Administration (FDA) reviewed the SAP (Version 1.0, dated 05 March 2021) and advised the applicant to clarify the testing plan of OS.

Secondly, there were changes to the OS testing procedure in the SAP during this open-label trial. The change was made in May 2021, 3-4 months prior to the clinical data cut-off on 06 September 2021. The applicant justified the changes by comments made by the FDA (no data from the ongoing study was used to inform the changes made).

As neither the interim nor the final OS analysis showed a statistically significant effect on OS (see under Efficacy data and additional analyses), there is no impact of the late definition of the multiplicity procedure on the interpretation of the OS analysis. Based on this, it is considered that the internal validity of the study was maintained irrespective of the changes in the testing procedures and that the presented efficacy results do allow for an adequate B/R assessment.

In addition, one patient was accidentally excluded from the analysis. The subject consented to the study and was successfully randomised to fulvestrant. The subject subsequently relocated and

transferred care and study participation to another centre. A thorough quality review of the clinical database was conducted and no additional data issues were identified. Additional analyses based on the updated datasets (N=478, including missing subject) were provided and the PFS estimates (medians, hazard ratios etc.) remained unchanged.

Efficacy data and additional analyses

Patient disposition- A total of 695 patients were screened and 478 were randomised, 239 to the elacestrant arm and 239 to the SOC arm at the data cut-off (DCO) of 06 September 2021. The majority of patients in the SOC group received fulvestrant (69%). Among *ESR1*-mut patients, 115 were randomised to elacestrant and 113 to SOC.

Protocol deviations- The number of major protocol deviations was small in both groups (n=6 in the elacestrant group and n=11 in the SOC group, mainly due to being randomised and not treated) and the impact of these on efficacy was assessed with the modified per protocol analysis.

Baseline characteristics- Baseline demographic and disease characteristics were, in general, balanced across the treatment arms for the overall and *ESR1*-mut population. The median age of patients in the overall population was 63-64 years. Most patients were women (99%) and most patients were white (87.8%). While the proportion of men in the study programme is very low, it is still considered possible to extrapolate results to men, based on the common biological and pharmacological rationale. All female patients were postmenopausal. All but 1 patient had an ECOG performance status of 0 or 1. Most patients had ductal tumour histology (65.3%). Metastatic sites were most commonly in the bone (78.9% [bone only: 14.0%]), liver (49.6%), lymph nodes (28.5%), and lung (26.2%). The information regarding the M1 stage at baseline was conflicting with >60% of missing data, possibly due to misunderstandings by investigators. Brain metastases were uncommon (1.5%). Baseline demographic and disease characteristics for those with *ESR1*-mut tumours were generally representative of the broader study population. When comparing baseline disease characteristics of overall population and *ESR1*-mut population, patients with *ESR1*-mutation had a shorter disease duration at study entry, which was most obvious in the elacestrant-treatment group.

Regarding prior systemic anticancer therapy, about 20-25% of patients received 1 line of chemotherapy and 40%-46% received 2 lines of endocrine therapy in the advanced/metastatic setting. All patients were previously treated with a CDK4/6i. Around 80% received prior AI and 30% prior fulvestrant. Most of the patients received prior AI only and the chosen SOC in the control arm was acceptable for most patients. For patients treated with prior fulvestrant, one patient received fulvestrant again, not in line with the protocol guidance. For all 35 patients who received prior AI and fulvestrant, the SOC also may not have been optimal, as prior treatment was repeated as 'SOC' treatment in the study. However, this concerns a relatively small number of patients in the SOC treatment arm (36/239 patients; 15.1%) for whom treatment may not have been optimal. It is also reassuring, that the number of discontinuations due to AEs did not differ much in the elacestrant versus SOC arms (see 2.6.8.), meaning that the choice for the SOC was acceptable safety wise.

Primary endpoint: IRC-assessed PFS overall and *ESR1*-mut population

As of the DCO of 06 September 2021, 18 patients in the elacestrant group and 6 patients in the SOC group were still on treatment. The most common reason for treatment discontinuation was investigator-assessed progression per RECIST in about 75% of patients.

In the overall population, PFS was statistically significantly improved for elacestrant compared to SOC (p=0.0018, stratified log-rank test) with HR of 0.70 (95% CI: 0.55-0.88). Median PFS was 2.79 months in the elacestrant group versus 1.91 months in the SOC group. For *ESR1*-mut patients, PFS

was also statistically significantly improved in patients randomised to elacestrant compared to SOC (p=0.0005, stratified log-rank test) with HR of 0.55 (95% CI: 0.39-0.77). Median PFS was 3.78 months in the elacestrant group versus 1.87 months in the SOC group. The higher p-value was <0.0475; thus, both primary objectives were met with statistical significance under the multiplicity correction methods used for this study. Although significant, the improvement in median IRC-assessed PFS was small. The increase in elacestrant compared to SOC was 0.9 month in the overall population and 1.9 month in the *ESR1*-mutated population (as measured in the median). Results showed that the activity of further endocrine monotherapy is very limited in this patient population with prior endocrine treatment lines including a combination with CDK4/6i. Also, the PFS results showed considerably smaller effects than the assumptions (i.e. median PFS of 5.3 months for SOC and 8.7 months for elacestrant).

The presented results were based on the final PFS analysis with less events than prespecified in the SAP for the final analysis (see section above on study conduct). In order to determine whether the results of the earlier than planned analysis could be assessed, the applicant performed additional PFS analyses. The HR in the overall population was between 0.614 and 0.669 between February and July 2021, which was consistent with the HR of 0.697 at the final PFS analysis (06 September 2021). No analysis was performed with adjustment of the p-value for earlier testing than planned, but a calculation showed that an O'Brien-Flemming two-sided boundary at 300 as an interim analysis to a final analysis with 340 events for the planned final analysis would be 0.03216 (instead of 0.0475). This would leave the current actual final analysis still statistically significant. Also, an update of the PFS analyses with a data cut-off date of 02 September 2022 (the same cut-off date for the OS analysis, providing approximately one additional year of follow-up) was provided. At that time 7 additional PFS events were observed, leading to a total of 307 events, relative to the original cut-off date of 06 September 2021. Median PFS at the updated analysis was 2.79 months in the elacestrant arm and 1.91 months in the SOC with a HR of 0.696 for this updated PFS analysis, compared with 0.697 in the final PFS analysis. Within the *ESR1*-mut population, the number of PFS events in the elacestrant arm increased from 62 to 67 and in the SOC arm from 78 to 80. The HR changed from 0.546 to 0.543 in the updated analysis with a median PFS of 3.78 months in patients treated with elacestrant and 1.87 months in the patient group treated with SOC. With the provision of HR ratios over time and the updated PFS analysis, the final PFS analysis (06 September 2021) is regarded a reliable alternative to the originally planned final analysis.

The PFS KM curves in both arms in the overall and *ESR1*-mut population showed a stark drop at the time of the first tumour assessment (week 8). On the 70 patients in the overall population with PFS <7 weeks, 24 patients in the elacestrant and 46 patients in the SOC arm had a progression event or censoring <7 weeks as assessed by blinded IRC. In both arms, around 65-70% were censored and around 30-35% had an event. In retrospect, the timing of the first tumour assessment was not optimal. The first scan might have been taken too early given the mechanism of action of endocrine therapy or too late to see efficacy before the first assessment as the duration of PFS was much shorter than anticipated. This drop in PFS is reported in patients who progressed on a CDK4/6i and were treated with fulvestrant (Lindeman et al., Clinical Cancer Research, 2022) and the control arm in Study 308 was less active than expected. It also means that one dimensional measure such as the HR and the restricted mean survival time (RMST) do not capture the fact that for a substantial part of the patients (~50%) efficacy cannot be observed (those progressing before 8 weeks fall in a plateau at ~100% or have similar survival). Separation of PFS curves can only be ascertained at and after 8 weeks. Limited follow-up is available and PFS curves are uncertain after 8 months due to extensive censoring.

Landmark analysis of PFS rates are difficult to interpret due to the overall low number of patients at risk after 8 weeks, especially after 6 months when less than 20% of the population is still event-free.

At 3 months there was a difference of about 10% in the overall population and 16% in the *ESR1*-mut population in favour of elacestrant.

Exploratory PFS analyses by type of detected *ESR1*-mutation for the most important /frequent deleterious or suspected deleterious *ESR1* mutations were submitted. The most often occurring mutations, regardless of the number of mutations detected per patient, were D538G, Y537S, Y537N, E380Q, L536H, and Y537C. For these mutations, median PFS was (numerically) longer for elacestrant compared to SOC. The other mutations occurred in a low number of patients, hampering efficacy analyses per these mutations.

The applicant performed prespecified sensitivity analyses, of which results were supportive of the primary analysis. Additional post hoc sensitivity analyses (interval censored analysis and an analysis with PFS events dated at the next planned visit in case of unscheduled assessment) supported that a difference in PFS exists despite the strong interval-censored character (step shape) of PFS. Sensitivity analyses for the start of new anticancer therapy and tipping point analyses for early censoring were provided. Results from the sensitivity analyses were in line with the final PFS analysis. In total, 7 patients received new anticancer therapy. Sensitivity analyses where the start of new anticancer thrapy was reported as an event, showed a HRs in line with the final PFS analysis. Regarding earlier censoring, 30.1% of the elacestrant and 33.5% of the SOC treated patients were censored in the first 2 months. For the tipping point analysis, two approaches were performed. With the first approach, HR never reached 1 for the overall and *ESR1*-mut population. The second approach demonstrated that with all the first censored patients transformed into an event, HR was 0.923 in all patients and 0.808 in *ESR1*-mut patients. When continuing adding transformed events one by one after 2 months, the tipping point was between 55-60 patients in the overall patient population and HR never reached '1' in the *ESR1*-mut population. The tipping point analysis suggested the results in the *ESR1*-mut population are more robust than in the overall population.

Key secondary endpoint: OS overall and *ESR1*-mut population

At the presented interim analysis, OS was not statistically different between the elacestrant and SOC arms in both the overall and *ESR1*-mut population (alpha 0.0001). Median OS was not reached in the overall population in the elacestrant and SOC arm (HR: 0.742 (95%CI: 0.536-1.025)). For the *ESR1*-mut population median was not reached with elacestrant (95%CI: 18.60-NE) and 16.95 months (95%CI: 14.00-NE) with the SOC, respectively (HR: 0.592 (95%CI:0.361-0.958)). The KM curves did not suggest a detriment for elacestrant, although the curves are difficult to interpret after 8 months due to censoring. Final OS analysis at 51% of events with a cut-off date of 02 September 2022 reported a median OS of 24.61 in the elacestrant and 22.57 months in the SOC arm for all patients with overlapping 95% and HR 0.912. In *ESR1*-mut patients, median OS was 24.18 and 23.49 months, respectively, with HR 0.903. The Kaplan-Meier plots showed that the curves in the ITT and the *ESR1*-mut were visually in favour of the elacestrant arm up to the point of 24 months at which time heavy censoring started. The difference between the elacestrant and SOC arms was larger in the *ESR1*-mut population compared to the ITT. Furthermore, it is not negligible that in the *ESR1*-mut population for 13.9% and 12.4% (elacestrant and SOC) the information on OS is lacking. For a pivotal trial in which OS is the most important secondary endpoint, it is expected that all measures are taken to ensure completeness of survival follow-up. The applicant committed to complete the overall survival information on all patients still in follow-up in Study 308 and analyse the completed overall survival data (REC). The sensitivity analysis for OS to examine the censoring patterns did not reveal signs of attrition bias.

Secondary endpoint: IRC-assessed PFS and OS in *ESR1*-mut-nd population

Median PFS was similar in the elacestrant and SOC arm in the *ESR1*-mut-nd population and KM curves largely overlapped. KM-curves beyond 2 months are difficult to interpret due to the limited number of

patients (still at risk). A possible issue is that the *ESR1*-mut-nd population contains both patients who have proven WT disease and patients in whom the test could not be performed, but the number of patients in whom *ESR1* mut testing could not be performed was very low. In only three patients in the elacestrant arm and a single patient in the SOC arm, the mutation status could not be assessed. IRC-assessed PFS analysis in only *ESR1*-wild type patients, showed a similar median PFS between elacestrant (1.94 months) and SOC arm (1.97 months) with the upper bound for the 95% CI of the HR crossing 1.

No difference in OS was found between elacestrant and SOC in the *ESR1*-mut-nd population with overlapping KM curves. Curves can only be interpreted up to 8 months due to the extensive censoring.

The clinical significance in the overall population appears limited and mainly a reflection of effects in the *ESR1*-mut population whereas it is unclear if patients in ESR1-mut-nd population really benefit. In view that results for the SOC treatment are at a low level of efficacy, the indication was revised to be restricted to the *ESR1*-mut population.

Secondary endpoint: investigator-assessed PFS

Differences between median investigator-assessed PFS for elacestrant and SOC were lower than per independent review for the overall population, *ESR1*-mut population, and *ESR1*-mut-nd population. KM curves only showed a separation in the *ESR1*-mut population. The investigator-assessed PFS does, therefore, not support the benefit in PFS per IRC in the overall population which further supports the restriction to the *ESR1*-mut population.

Discordance was observed between the independent and investigator review of PFS. In the overall population 32.6% in the elacestrant group and 22.7% in the SOC group were assessed as having PD by the investigators (and will have discontinued treatment) but were not yet considered to have PD by the IRC at the time of assessment of PD by the investigator. In the IRC PFS analysis, these patients are counted as "censored without progression" or, if they subsequently died, to have had a PFS event at the time of death. Because possibly informative censoring (when investigators assessed progression without IRC progression) occurred more often in the elacestrant arm than in the control arm, the IRC PFS may be biased in favour of the elacestrant arm. Sensitivity analyses in which both investigator- and IRC-assessed progression were counted as events were performed. In the overall population this led to a median PFS of 1.94 months in the elacestrant arm and 1.87 months in the control arm (HR 0.774). For the *ESR1*-mut population, median PFS was 2.00 months in the elacestrant and 1.87 months in the SOC arm (HR 0.643). Even though these differences might be statistically significant, the absolute differences in median PFS are very small and of doubtful clinical relevance. The issue of informative censoring when investigators assessed progression without IRC progression, therefore, remains an uncertainty. However, it is acknowledged that for the *ESR1*-mut population a gain in median PFS of 1.58 months was reported for investigator-assessed PFS in favour of elacestrant, which was absent in the overall population (difference in median PFS of only 0.17 months).

Other secondary efficacy endpoints: ORR and clinical benefit rate (CBR) did not show differences between treatment arms in any population. Duration of response (DoR) was not reached when assessed per independent review, but overall the number of patients with a response was low, making interpretation of DoR difficult.

Patient-reported outcomes: There were no noteworthy differences between the treatment groups and no noteworthy changes over time in either group. Considering that no formal statistical testing was planned and hypothesis and handling of missingness were not provided, PRO data may be subject to bias and are thus not included in the SmPC,

Exploratory endpoints: Comparable number of patients received chemotherapy as first systemic therapy after treatment discontinuation, though numbers were somewhat lower in the *ESR1*-mut population. Elacestrant did not delay time to chemotherapy compared to SOC.

No results were provided for the exploratory endpoints on biomarker analyses. Only very limited on- and post-treatment biopsies were collected and no tissue analyses were performed and no ctDNA analyses are currently planned. Considering the rather modest efficacy of elacestrant, the results of biomarker analyses to better select patients who will benefit the most are considered of great value.

The applicant will perform a biomarker analysis in the ongoing studies (ELEVATE [NCT05563220], ELECTRA [NCT04791384], and ELCIN [NCT05596409]), in particular, ctDNA analysis on plasma samples, using a panel of relevant genes, at the baseline and longitudinally during the patient treatment (REC).

Subgroup analyses: Prespecified subgroup IRC-assessed PFS analyses for baseline characteristics in the overall and *ESR1*-mut population showed HRs<1, except for race Asian and Other in the overall population, although the subgroups were small.

Regarding the stratification factors, the results previously discussed showed that efficacy is driven by the *ESR1*-mut population. The subgroups of patients with and without prior fulvestrant are considered relevant as fulvestrant and elacestrant share a common mechanism of action and previous therapy could be an effect modifier. Subgroup analysis in patients with or without prior fulvestrant showed comparable HRs of 0.67, but medians for PFS were overlapping for patients with prior fulvestrant and not in patients without prior fulvestrant. Acknowledging that this concerns an exploratory analysis, this suggests that efficacy is lower in patients with prior fulvestrant.

In addition, post hoc analyses comparing IRC-assessed PFS of all patients receiving elacestrant to patients receiving fulvestrant or AIs in the SOC arm were provided. The majority of patients in the SOC group received fulvestrant (69%). Both the HR for PFS and the differences in median PFS were similar in magnitude to those observed in the primary analysis for the SOC patients who received fulvestrant. As was observed in the primary analysis, there was a higher effect of elacestrant in the *ESR1*-mut population and no effect in *ESR1*-mut-nd patients. When comparing elacestrant to AI, the 95% CI for HR was containing 1 in all populations, i.e. the overall, *ESR1*-mut, and *ESR1*-mut-nd populations. Interpretation of results is hampered by the low numbers and non-randomised comparisons in some populations.

In *ESR1*-mut patients with no prior fulvestrant (n=82) a direct comparison of fulvestrant and elacestrant is possible. For fulvestrant a 6-month PFS rate of 21.0 % per IRC (19.4% by INV) was reported. For elacestrant a 6-month PFS rate of 42.4 % per IRC (33.4% by INV) was reported. Thus, the treatment effect of elacestrant was a difference in 6-month PFS rate of 21.4 % by IRC or 14.0% by INV. For 12-month PFS rates similar differences were reported. This suggests that elacestrant treatment is not a disadvantage to fulvestrant in the subgroup with no prior fulvestrant and the observed differences in *ESR1*-mut patients are not purely driven by the AI group.

The interpretation of OS subgroup analyses for the ITT and *ESR1*-mut population is limited by the sample size. Some of the subgroups showed a point estimate of the HR above 1, e.g. in the *ESR1*-mut population for the subgroups with no visceral metastases, age <65 years, age <75 years, race Asian, race Other, region North America, baseline ECOG PS 0, measurable disease at baseline and 1 prior line of endocrine therapy in the advanced/metastatic setting. Reassuringly, in all cases the 95% confidence interval was wide and the lower bound was well below 1.

2.6.7. Conclusions on the clinical efficacy

The primary endpoint IRC-assessed PFS shows significant, but small differences in favour of elacestrant compared to SOC in the overall population and the population with an *ESR1* mutation. The results seem to be mainly driven by patients with an *ESR1* mutation who have a longer PFS in the elacestrant group compared to the overall population, but the SOC performs similar in the *ESR1*-mut and overall group. Therefore, the indication was restricted to patients with an activating *ESR1*-mutated tumour. The differences in PFS were only observed at and after the first scan at 8 weeks, but tipping point analyses correcting for early censoring, showed that in the *ESR1*-mut population the results are robust.

The key secondary endpoint OS was not statistically different between the elacestrant and SOC arms in both the overall and *ESR1*-mut population, though reassuringly the KM curves did not show signals of a detriment.

During the study, two major changes were conducted regarding the efficacy testing procedures. The first change was an earlier than planned PFS analysis. Although the decision for changing the analysis time point seems to have been made by persons not blinded to treatment assignment, these had no access to aggregated data. In addition, additional analyses with an updated PFS analysis and stable HR ratios over time support that the final PFS analysis provided can be regarded as a reliable alternative to the originally planned final analysis. Regarding the second amendment, the OS testing procedure was changed late in an open-label study. This change was motivated by external advice from the FDA and no data from the ongoing study was used to inform the changes made. As neither the interim nor the final OS analysis showed a statistically significant effect on OS, there is also no impact of the late definition of the multiplicity procedure on the interpretation of the OS analysis. Based on this, it is considered that the internal validity of the study was maintained irrespective of the changes in the testing procedures and that the presented efficacy results do allow for an adequate B/R assessment.

An additional issue identified is the discordance between independent and investigator review of PFS with the risk of informative censoring biasing IRC-assessed PFS in the elacestrant arm. A sensitivity analysis counting both investigator- and IRC-assessed progression as event showed a very small difference between the elacestrant and SOC arm, even in the *ESR1*-mutated population. However, with the restriction of the indication to *ESR1*-mut patients and the gain of median PFS of 1.58 months reported for investigator-assessed PFS in favour of elacestrant in this subpopulation, this issue will not be further pursued. A sensitivity analysis where the start of new anticancer therapy was reported as event was in line with the final PFS analysis.

The applicant is recommended (REC) to:

- perform biomarker studies in ongoing and future elacestrant studies to better select patients who will benefit the most, i.e in the ongoing studies (ELEVATE [NCT05563220], ELECTRA [NCT04791384], and ELCIN [NCT05596409]);

- complete the overall survival information on all patients who are not lost to follow-up in Study 308 and to analyse the completed overall survival data.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Overall, as of 27 December 2021, a total of 815 subjects were exposed to elacestrant across all completed studies, which included besides mBC, several studies in healthy subjects and 2 phase 2

studies in postmenopausal women with vasomotor symptoms. The dose range studied was 200 mg – 1000 mg, most subjects received 400 mg. As of 06 September 2021, a total of 312 subjects with mBC were exposed to elacestrant; 239 subjects from the Phase 3 Study 308, 57 subjects from the completed Phase 1 Study 005, and 16 subjects from the completed Phase 1 Study 106. Most subjects received 400 mg, 4 subjects in study 005 received 200 mg and 3 subjects received 600 mg. In Study 006, 2 subjects received 200 mg only.

Safety data were presented for the proposed registration dose for elacestrant of 400 mg QD for both the pooled phase 1 (RAD1901-105 and RAD1901-106) studies (n=64) and the phase 3 RAD1901-308 study (n=237) separately, as subjects enrolled in the Phase 1 studies were more heavily pre-treated and with more advanced disease and 40 subjects received the initial capsule formulation.

Median exposure for elacestrant was 117.0 days (range: 5-1288) and 84.0 days (range: 13-756) for the phase 1 Pool and Study 308, respectively. The median duration of treatment was 85 days (range 5 to 1288). Median exposure for the SOC was fulvestrant was 84.0 days (range: 2-464) and for AIs 64.5 days (1-554). Relative dose intensity was above 90% for 97%-100% of subjects across studies and treatment arms.

2.6.8.2. Adverse events

An overview of the treatment-emergent adverse events (TEAEs) is shown in Table 69.

Table 69 Overview of TEAEs (Safety population)

	Studies 005 and 106			Study 308			
					SOC		
	Elacestrant 400 mg Capsules (N = 40)	Elacestrant 400 mg Tablets (N = 24)	Elacestrant 400 mg Overall (N = 64)	Elacestrant 400 mg Tablets (N = 237)	Fulvestrant (N = 161)	AIs (N = 68)	SOC Total (N = 229)
Number of subjects with at least 1 TEAE	39 (97.5)	22 (91.7)	61 (95.3)	218 (92.0)	144 (89.4)	53 (77.9)	197 (86.0)
Any treatment-related TEAEs	37 (92.5)	19 (79.2)	56 (87.5)	150 (63.3)	72 (44.7)	28 (41.2)	100 (43.7)
Any NCI CTCAE Grade 3 and Grade 4 TEAEs	15 (37.5)	10 (41.7)	25 (39.1)	64 (27.0)	33 (20.5)	14 (20.6)	47 (20.5)
Any treatment-related NCI CTCAE Grade 3 and Grade 4 TEAEs	8 (20.0)	1 (4.2)	9 (14.1)	17 (7.2)	5 (3.1)	2 (2.9)	7 (3.1)
Any fatal (Grade 5) TEAEs	1 (2.5)	1 (4.2)	2 (3.1)	4 (1.7)	5 (3.1)	1 (1.5)	6 (2.6)
Any treatment-related fatal (Grade 5) TEAEs	0	0	0	0	0	0	0
Any serious TEAEs	7 (17.5)	8 (33.3)	15 (23.4)	29 (12.2)	15 (9.3)	10 (14.7)	25 (10.9)
Any treatment-related serious TEAEs	1 (2.5)	1 (4.2)	2 (3.1)	3 (1.3)	0	0	0
Any TEAEs leading to dose interruption	12 (30.0)	8 (33.3)	20 (31.3)	36 (15.2)	5 (3.1)	7 (10.3)	12 (5.2)
Any treatment-related TEAEs leading to dose interruption	8 (20.0)	1 (4.2)	9 (14.1)	15 (6.3)	0	4 (5.9)	4 (1.7)
Any TEAEs leading to dose reduction	0	0	0	7 (3.0)	0	NA	0
Any treatment-related TEAEs leading to dose reduction	0	0	0	6 (2.5)	0	NA	0
Any TEAEs leading to discontinuation of study drug	7 (17.5)	1 (4.2)	8 (12.5)	15 (6.3)	6 (3.7)	4 (5.9)	10 (4.4)
Any treatment-related TEAEs leading to discontinuation of study drug	6 (15.0)	0	6 (9.4)	8 (3.4)	1 (0.6)	1 (1.5)	2 (0.9)

Abbreviations: AI = aromatase inhibitor; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic case report form; ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in group; NA = not applicable; NCI = National Cancer Institute; SOC = standard of care; TEAE = treatment-emergent adverse event.

Note: MedDRA Version 23.0 was used; NCI CTCAE Version 4.3 was used for Studies 005 and 106, and NCI CTCAE Version 5.0 was used for Study 308. If a subject experienced more than 1 event in a given category, that subject was counted only once in that category. A TEAE was considered treatment related if its causality was "possibly related," "definitely related," or "related" on the AE eCRF pages from each study.

Common AEs

A summary of TEAES occurring in ≥5% of subjects overall by PT is presented in Table 70. Overall, most subjects (>30%) treated with elacestrant reported a TEAE in the SOC Gastrointestinal Disorders (65.4%), followed by Musculoskeletal and connective tissue disorders (44.7%), General disorders and administration site conditions (37.6%), and Investigations (34.2%).

The most frequently reported TEAEs (≥10%) for elacestrant per PT were nausea (35.0% vs 16.1% with fulvestrant vs 25.0% with AI), vomiting (19.0% vs 7.5% with fulvestrant vs. 10.3% with AI), and fatigue (19.0% vs. 21.7% with fulvestrant vs. 11.8% with AI). Other commonly (≥10%) observed adverse events with elacestrant were decreased appetite, back pain, arthralgia, diarrhoea, aspartate aminotransferase increased (AST), constipation, headache, hot flush, and dyspepsia. GI TEAEs, except diarrhoea, were more frequently reported than for the SOC. Frequencies of other TEAEs were in general in the same order of magnitude as for the SOC. AEs reported more frequently (≥5% difference) with fulvestrant compared to elacestrant were injection site pain (8.7%) related to the i.m. route of administration and blood pressure increased for AI (8.8% vs. 3.8%). Common TEAEs for the SOC are in line with that known and reported in the SmPCs.

Table 70 Treatment-emergent adverse events in ≥5% of subjects in any Study 308 group (Safety population)

System Organ Class Preferred Term[a]	Studies 005 and 106				Study 308			
	Elacestrant 400 mg Capsules (N = 40)	Elacestrant 400 mg Tablets (N = 24)	Elacestrant 400 mg Overall (N = 64)		Elacestrant 400 mg Tablets (N = 237)	SOC		
						Fulvestrant (N = 161)	AIs (N = 68)	SOC Total (N = 229)
Subjects with any TEAEs	39 (97.5)	22 (91.7)	61 (95.3)		218 (92.0)	144 (89.4)	53 (77.9)	197 (86.0)
Gastrointestinal disorders	**36 (90.0)**	**19 (79.2)**	**55 (85.9)**		**155 (65.4)**	**50 (31.1)**	**28 (41.2)**	**78 (34.1)**
Nausea	26 (65.0)	8 (33.3)	34 (53.1)		83 (35.0)	26 (16.1)	17 (25.0)	43 (18.8)
Vomiting	17 (42.5)	4 (16.7)	21 (32.8)		45 (19.0)	12 (7.5)	7 (10.3)	19 (8.3)
Diarrhoea	11 (27.5)	3 (12.5)	14 (21.9)		33 (13.9)	14 (8.7)	9 (13.2)	23 (10.0)
Constipation	6 (15.0)	5 (20.8)	11 (17.2)		29 (12.2)	10 (6.2)	5 (7.4)	15 (6.6)
Dyspepsia	18 (45.0)	5 (20.8)	23 (35.9)		24 (10.1)	4 (2.5)	2 (2.9)	6 (2.6)
Abdominal pain	4 (10.0)	2 (8.3)	6 (9.4)		15 (6.3)	7 (4.3)	7 (10.3)	14 (6.1)
General disorders and administration site conditions	**23 (57.5)**	**11 (45.8)**	**34 (53.1)**		**89 (37.6)**	**70 (43.5)**	**19 (27.9)**	**89 (38.9)**
Fatigue	16 (40.0)	5 (20.8)	21 (32.8)		45 (19.0)	35 (21.7)	8 (11.8)	43 (18.8)
Injection site pain	0	0	0		0	14 (8.7)	0	14 (6.1)
Asthenia	0	0	0		22 (9.3)	14 (8.7)	5 (7.4)	19 (8.3)
Metabolism and nutrition disorders	**6 (15.0)**	**6 (25.0)**	**12 (18.8)**		**42 (17.7)**	**14 (8.7)**	**9 (13.2)**	**23 (10.0)**
Decreased appetite	6 (15.0)	3 (12.5)	9 (14.1)		35 (14.8)	12 (7.5)	9 (13.2)	21 (9.2)
Musculoskeletal and connective tissue disorders	**19 (47.5)**	**12 (50.0)**	**31 (48.4)**		**106 (44.7)**	**71 (44.1)**	**31 (45.6)**	**102 (44.5)**
Arthralgia	6 (15.0)	4 (16.7)	10 (15.6)		34 (14.3)	28 (17.4)	9 (13.2)	37 (16.2)
Back pain	7 (17.5)	4 (16.7)	11 (17.2)		33 (13.9)	16 (9.9)	6 (8.8)	22 (9.6)
Pain in extremity	4 (10.0)	3 (12.5)	7 (10.9)		18 (7.6)	9 (5.6)	5 (7.4)	14 (6.1)
Bone pain	0	0	0		15 (6.3)	8 (5.0)	7 (10.3)	15 (6.6)
Musculoskeletal chest pain	2 (5.0)	1 (4.2)	3 (4.7)		14 (5.9)	6 (3.7)	1 (1.5)	7 (3.1)
Musculoskeletal pain	4 (10.0)	2 (8.3)	6 (9.4)		11 (4.6)	9 (5.6)	4 (5.9)	13 (5.7)
Myalgia	1 (2.5)	5 (20.8)	6 (9.4)		11 (4.6)	13 (8.1)	4 (5.9)	17 (7.4)

System Organ Class Preferred Term[a]	Studies 005 and 106				Study 308			
	Elacestrant 400 mg Capsules (N = 40)	Elacestrant 400 mg Tablets (N = 24)	Elacestrant 400 mg Overall (N = 64)		Elacestrant 400 mg Tablets (N = 237)	SOC		
						Fulvestrant (N = 161)	AIs (N = 68)	SOC Total (N = 229)
Investigations	**19 (47.5)**	**15 (62.5)**	**34 (53.1)**		**81 (34.2)**	**58 (36.0)**	**23 (33.8)**	**81 (35.4)**
Aspartate aminotransferase increased	9 (22.5)	3 (12.5)	12 (18.8)		31 (13.1)	20 (12.4)	8 (11.8)	28 (12.2)
Alanine aminotransferase increased	6 (15.0)	3 (12.5)	9 (14.1)		22 (9.3)	17 (10.6)	6 (8.8)	23 (10.0)
Blood cholesterol increased	4 (10.0)	4 (16.7)	8 (12.5)		16 (6.8)	7 (4.3)	0	7 (3.1)
Blood alkaline phosphatase increased	3 (7.5)	3 (12.5)	6 (9.4)		15 (6.3)	10 (6.2)	6 (8.8)	16 (7.0)
Blood pressure increased	6 (15.0)	2 (8.3)	8 (12.5)		9 (3.8)	6 (3.7)	6 (8.8)	12 (5.2)
Blood glucose increased	7 (17.5)	4 (16.7)	11 (17.2)		6 (2.5)	9 (5.6)	3 (4.4)	12 (5.2)
Nervous system disorders	**12 (30.0)**	**13 (54.2)**	**25 (39.1)**		**55 (23.2)**	**37 (23.0)**	**19 (27.9)**	**56 (24.5)**
Headache	4 (10.0)	5 (20.8)	9 (14.1)		29 (12.2)	18 (11.2)	8 (11.8)	26 (11.4)
Vascular disorders	**9 (22.5)**	**5 (20.8)**	**14 (21.9)**		**33 (13.9)**	**18 (11.2)**	**5 (7.4)**	**23 (10.0)**
Hot flush	7 (17.5)	4 (16.7)	11 (17.2)		27 (11.4)	15 (9.3)	4 (5.9)	19 (8.3)
Blood and lymphatic system disorders	**9 (22.5)**	**4 (16.7)**	**13 (20.3)**		**41 (17.3)**	**20 (12.4)**	**10 (14.7)**	**30 (13.1)**
Anaemia	7 (17.5)	3 (12.5)	10 (15.6)		22 (9.3)	11 (6.8)	6 (8.8)	17 (7.4)
Lymphocyte count decreased	2 (5.0)	2 (8.3)	4 (6.3)		12 (5.1)	3 (1.9)	2 (2.9)	5 (2.2)
Psychiatric disorders	**6 (15.0)**	**7 (29.2)**	**13 (20.3)**		**34 (14.3)**	**19 (11.8)**	**7 (10.3)**	**26 (11.4)**
Insomnia	1 (2.5)	2 (8.3)	3 (4.7)		18 (7.6)	8 (5.0)	3 (4.4)	11 (4.8)
Anxiety	1 (2.5)	4 (16.7)	5 (7.8)		9 (3.8)	2 (1.2)	3 (4.4)	5 (2.2)
Depression	2 (5.0)	0	2 (3.1)		6 (2.5)	5 (3.1)	4 (5.9)	9 (3.9)
Respiratory, thoracic and mediastinal disorders	**15 (37.5)**	**8 (33.3)**	**23 (35.9)**		**46 (19.4)**	**27 (16.8)**	**10 (14.7)**	**37 (16.2)**
Dyspnoea	5 (12.5)	2 (8.3)	7 (10.9)		18 (7.6)	8 (5.0)	7 (10.3)	15 (6.6)
Cough	6 (15.0)	4 (16.7)	10 (15.6)		15 (6.3)	11 (6.8)	1 (1.5)	12 (5.2)
Infections and infestations	**12 (30.0)**	**9 (37.5)**	**21 (32.8)**		**43 (18.1)**	**23 (14.3)**	**10 (14.7)**	**33 (14.4)**
Urinary tract infection	2 (5.0)	5 (20.8)	7 (10.9)		16 (6.8)	7 (4.3)	5 (7.4)	12 (5.2)

System Organ Class Preferred Term[a]	Studies 005 and 106				Study 308			
	Elacestrant 400 mg Capsules (N = 40)	Elacestrant 400 mg Tablets (N = 24)	Elacestrant 400 mg Overall (N = 64)		Elacestrant 400 mg Tablets (N = 237)	SOC		
						Fulvestrant (N = 161)	AIs (N = 68)	SOC Total (N = 229)
Skin and subcutaneous tissue disorders	**11 (27.5)**	**3 (12.5)**	**14 (21.9)**		**45 (19.0)**	**12 (7.5)**	**12 (17.6)**	**24 (10.5)**
Rash	1 (2.5)	0	1 (1.6)		10 (4.2)	1 (0.6)	5 (7.4)	6 (2.6)

Abbreviations: AE = adverse event; AI = aromatase inhibitor; ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in group; SOC = standard of care; TEAE = treatment-emergent adverse event.

[a] Preferred terms are summarized using AE synonym terms.

Note: MedDRA Version 23.0 was used. Subjects with 1 or more AEs within a system organ class of MedDRA were counted only once. System organ classes are sorted by descending order of frequency of preferred terms in the elacestrant group in Study 308. Preferred terms are sorted by descending order of frequency in the elacestrant group in Study 308 within each system organ class.

Source: ISS, Table 14.3.1.2 and Study 308, Table 14.3.1.2.1.2.

Most TEAEs were Grade 1 or 2; 27.0% in the elacestrant arm and 20.5% in the SOC were Grade 3 or 4. Most commonly reported Grade 3 or 4 TEAEs with elacestrant were nausea, back pain, bone pain (2.5% each), alanine aminotransferase increased, and blood pressure increased (2.1% each). Most commonly reported Grade 3 or 4 TEAEs with fulvestrant were blood pressure increased (2.5%) and anaemia (1.2%). For AI, most commonly reported Grade 3 or 4 TEAEs were nausea, abdominal pain, blood pressure increased, gamma-glutamyltransferase increased, neutropenia, and tumour pain (2.9% each).

Treatment-related AEs

Gastrointestinal events were also the most frequently reported treatment-related TEAEs for elacestrant, mainly nausea (25.3%), and vomiting (11.0%) and at higher rates than for the SOC (Table 71). Fatigue was another frequently reported treatment-related TEAE (11.0%). The most common treatment-related TEAEs for fulvestrant were nausea (8.7%), fatigue (8.1%), and injection site pain (8.1%). The most common treatment-related TEAEs for AI were nausea (8.8%), decreased appetite (8.8%), and fatigue (7.4%). TEAEs in the SOC Musculoskeletal disorders and connective tissue were more often reported as treatment-related for the comparator arm (17.9% vs. 7.6%).

Table 71 Treatment-related TEAEs in ≥5% of subjects in any Study 308 group (Safety population)

System Organ Class Preferred Term[a]	Studies 005 and 106				Study 308			
	Elacestrant 400 mg Capsules (N = 40)	Elacestrant 400 mg Tablets (N = 24)	Elacestrant 400 mg Overall (N = 64)		Elacestrant 400 mg Tablets (N = 237)	SOC		
						Fulvestrant (N = 161)	AIs (N = 68)	SOC Total (N = 229)
Subjects with any treatment-related TEAEs	37 (92.5)	19 (79.2)	56 (87.5)		150 (63.3)	72 (44.7)	28 (41.2)	100 (43.7)
Gastrointestinal disorders	**35 (87.5)**	**11 (45.8)**	**46 (71.9)**		**102 (43.0)**	**18 (11.2)**	**11 (16.2)**	**29 (12.7)**
Nausea	23 (57.5)	7 (29.2)	30 (46.9)		60 (25.3)	14 (8.7)	6 (8.8)	20 (8.7)

System Organ Class Preferred Term[a]	Studies 005 and 106				Study 308			
	Elacestrant 400 mg Capsules (N = 40)	Elacestrant 400 mg Tablets (N = 24)	Elacestrant 400 mg Overall (N = 64)		Elacestrant 400 mg Tablets (N = 237)	SOC		
						Fulve-strant (N = 161)	AIs (N = 68)	SOC Total (N = 229)
Vomiting	14 (35.0)	2 (8.3)	16 (25.0)		26 (11.0)	4 (2.5)	2 (2.9)	6 (2.6)
Diarrhoea	6 (15.0)	0	6 (9.4)		18 (7.6)	5 (3.1)	3 (4.4)	8 (3.5)
Dyspepsia	17 (42.5)	4 (16.7)	21 (32.8)		14 (5.9)	0	2 (2.9)	2 (0.9)
Abdominal pain	2 (5.0)	0 (0.0)	2 (3.1)		4 (1.7)	0	4 (5.9)	4 (1.7)
General disorders and administration site conditions	**8 (20.0)**	**2 (8.3)**	**10 (15.6)**		**43 (18.1)**	**34 (21.1)**	**8 (11.8)**	**42 (18.3)**
Fatigue	7 (17.5)	1 (4.2)	8 (12.5)		26 (11.0)	13 (8.1)	5 (7.4)	18 (7.9)
Injection site pain	0	0	0		0	13 (8.1)	0	13 (5.7)
Vascular disorders	**6 (15.0)**	**3 (12.5)**	**9 (14.1)**		**23 (9.7)**	**11 (6.8)**	**3 (4.4)**	**14 (6.1)**
Hot flush	5 (12.5)	3 (12.5)	8 (12.5)		23 (9.7)	11 (6.8)	3 (4.4)	14 (6.1)
Metabolism and nutrition disorders	**4 (10.0)**	**2 (8.3)**	**6 (9.4)**		**19 (8.0)**	**1 (0.6)**	**6 (8.8)**	**7 (3.1)**
Decreased appetite	4 (10.0)	2 (8.3)	6 (9.4)		18 (7.6)	1 (0.6)	6 (8.8)	7 (3.1)
Nervous system disorders	**7 (17.5)**	**3 (12.5)**	**10 (15.6)**		**17 (7.2)**	**10 (6.2)**	**5 (7.4)**	**15 (6.6)**
Headache	3 (7.5)	2 (8.3)	5 (7.8)		10 (4.2)	8 (5.0)	2 (2.9)	10 (4.4)
Musculoskeletal disorders and connective tissue	**2 (5.0)**	**2 (8.3)**	**4 (6.3)**		**18 (7.6)**	**28 (17.4)**	**13 (19.1)**	**41 (17.9)**
Arthralgia	2 (5.0)	1 (4.2)	3 (4.7)		9 (3.8)	13 (8.1)	5 (7.5)	18 (7.9)
Myalgia	**0**	2 (8.3)	2 (3.1)		2 (0.8)	8 (5.0)	4 (5.9)	12 (5.2)

Abbreviations: AE = adverse event; AI = aromatase inhibitor; eCRF = electronic case report form; ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in group; SOC = standard of care; TEAE = treatment-emergent adverse event.

[a] Preferred terms are summarized using AE synonym terms.

Note: MedDRA Version 23.0 was used. Subjects with 1 or more AEs within a system organ class of MedDRA were counted only once. A TEAE is considered treatment related if its causality was "possibly related," "definitely related," or "related" on the AE eCRF pages from each study. System organ classes are sorted by descending order of frequency of preferred terms in the elacestrant group in Study 308. Preferred terms are sorted by descending order of frequency in the elacestrant group in Study 308 within each system organ class.

Sources: ISS, Table 14.3.1.3 and Study 308, Table 14.3.1.2.2.2.

Treatment-related TEAEs were seldom of high grade (7.2% for elacestrant and 3.1% for SOC). Grade 3 or 4 nausea with elacestrant was reported in 4 subjects (1.7%), other events (mainly SOC investigations) were reported in ≤2 subjects.

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

A summary of TEAEs with an outcome of death is shown in Table 72. Overall, frequencies were low; 1.7% (n=4) of subjects had a TEAE with an outcome of death in the elacestrant arm, compared to 2.6% (n=6) in the SOC. For each TEAE, only single cases were reported. None of the death cases were assessed as study drug related by the investigator.

Table 72 Treatment-emergent adverse events with an outcome of death (Safety population)

System Organ Class Preferred Term[a]	Studies 005 and 106			Study 308			
	Elacestrant 400 mg Capsules (N = 40)	Elacestrant 400 mg Tablets (N = 24)	Elacestrant 400 mg Overall (N = 64)	Elacestrant 400 mg Tablets (N = 237)	SOC		
					Fulvestrant (N = 161)	AIs (N = 68)	SOC Total (N = 229)
Subjects with any TEAEs of CTCAE Grade 5	1 (2.5)	1 (4.2)	2 (3.1)	4 (1.7)	5 (3.1)	1 (1.5)	6 (2.6)
Blood and lymphatic system disorders	**0**	**0**	**0**	**1 (0.4)**	**0**	**0**	**0**
Antiphospholipid syndrome	0	0	0	1 (0.4)	0	0	0
Cardiac disorders	**0**	**0**	**0**	**1 (0.4)**	**1 (0.6)**	**1 (1.5)**	**2 (0.9)**
Cardiac arrest	0	0	0	1 (0.4)	0	0	0
Arrhythmia	0	0	0	0	0	1 (1.5)	1 (0.4)
Myocardial infarction	0	0	0	0	1 (0.6)	0	1 (0.4)
Infections and infestations	**0**	**0**	**0**	**2 (0.8)**	**2 (1.2)**	**0**	**2 (0.9)**
Diverticulitis	0	0	0	1 (0.4)	0	0	0
Septic shock	0	0	0	1 (0.4)	0	0	0
COVID-19	0	0	0	0	1 (0.6)	0	1 (0.4)
Pneumonia	0	0	0	0	1 (0.6)	0	1 (0.4)
Gastrointestinal disorders	**0**	**0**	**0**	**0**	**1 (0.6)**	**0**	**1 (0.4)**
Gastric perforation	0	0	0	0	1 (0.6)	0	1 (0.4)
General disorders and administration site conditions	**1 (2.5)**	**1 (4.2)**	**2 (3.1)**	**0**	**0**	**0**	**0**
Disease progression[b]	1 (2.5)	1 (4.2)	2 (3.1)	0	0	0	0
Nervous system disorders	**0**	**0**	**0**	**0**	**1 (0.6)**	**0**	**1 (0.4)**
Ischaemic stroke	0	0	0	0	1 (0.6)	0	1 (0.4)

Abbreviations: AE = adverse event; AI = aromatase inhibitor; COVID-19 = coronavirus disease 2019; CTCAE = Common Terminology Criteria for Adverse Events; ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in group; SOC = standard of care; TEAE = treatment-emergent adverse event.

[a] Preferred terms are summarized using AE synonym terms.

[b] Identified as an AE in error, as disease progression should not be captured as an AE.

Note: MedDRA Version 23.0 was used. Subjects with 1 or more AEs within a system organ class of MedDRA were counted only once. System organ classes are sorted by descending order of frequency of preferred terms in the elacestrant group in Study 308. Preferred terms are sorted by descending order of frequency in the elacestrant group in Study 308 within each system organ class.

SAEs

Frequencies of SAEs were comparable between elacestrant and the SOC (12.2% vs. 10.9%). Serious TEAEs by PT occurring in more than 1 subject were nausea with elacestrant (1.3%), pneumonia with fulvestrant (1.2%), and abdominal pain and urinary tract infection (each 2.9%) with AI (

Table 73). Treatment-related serious TEAEs occurred only in the elacestrant arm in study 308 (1.3%). The only treatment-related serious TEAE reported in more than one subject was nausea (n=2, 0.8%). Treatment-related SAEs in the pooled phase 1 studies included one subject with acute hepatic failure (elacestrant 400 mg tablet), and one subject with pulmonary embolism and dyspnoea (elacestrant 400 mg capsules).

Table 73 Serious TEAEs in ≥1% of subjects in any study 308 group (Safety population)

System Organ Class Preferred Term	Studies 005 and 106			Study 308			
	Elacestrant 400 mg Capsules (N = 40)	Elacestrant 400 mg Tablets (N = 24)	Elacestrant 400 mg Overall (N = 64)	Elacestrant 400 mg Tablets (N = 237)	SOC		
					Fulvestrant (N = 161)	AIs (N = 68)	SOC Total (N = 229)
Subjects with any serious TEAEs	7 (17.5)	8 (33.3)	15 (23.4)	29 (12.2)	15 (9.3)	10 (14.7)	25 (10.9)
Gastrointestinal disorders	**1 (2.5)**	**1 (4.2)**	**2 (3.1)**	**6 (2.5)**	**0**	**3 (4.4)**	**3 (1.3)**
Nausea	0	0	0	3 (1.3)	0	0	0
Abdominal pain	0	0	0	0	0	2 (2.9)	2 (0.9)
Colitis	0	0	0	0	0	1 (1.5)	1 (0.4)
Diarrhoea	0	0	0	0	0	1 (1.5)	1 (0.4)
Enteritis	0	0	0	0	0	1 (1.5)	1 (0.4)
Ileus	0	0	0	0	0	1 (1.5)	1 (0.4)
Infections and infestations	**1 (2.5)**	**3 (12.5)**	**4 (6.3)**	**3 (1.3)**	**5 (3.1)**	**4 (5.9)**	**9 (3.9)**
Pneumonia	0	1 (4.2)	1 (1.6)	1 (0.4)	2 (1.2)	1 (1.5)	3 (1.3)
Sepsis	0	0	0	0	0	1 (1.5)	1 (0.4)
Urinary tract infection	0	0	0	0	0	2 (2.9)	2 (0.9)
Metabolism and nutrition disorders	**1 (2.5)**	**1 (4.2)**	**2 (3.1)**	**4 (1.7)**	**0**	**1 (1.5)**	**1 (0.4)**
Hypercalcaemia	0	0	0	1 (0.4)	0	1 (1.5)	1 (0.4)
Hypokalaemia	0	0	0	0	0	1 (1.5)	1 (0.4)
Musculoskeletal and connective tissue disorders	**0**	**0**	**0**	**5 (2.1)**	**1 (0.6)**	**1 (1.5)**	**2 (0.9)**
Pathological fracture	0	0	0	1 (0.4)	0	1 (1.5)	1 (0.4)
Cardiac disorders	**0**	**0**	**0**	**1 (0.4)**	**2 (1.2)**	**1 (1.5)**	**3 (1.3)**
Arrhythmia	0	0	0	0	0	1 (1.5)	1 (0.4)
General disorders and administration site conditions	**1 (2.5)**	**2 (8.3)**	**3 (4.7)**	**4 (1.7)**	**1 (0.6)**	**1 (1.5)**	**2 (0.9)**
Gait disturbance	0	0	0	0	0	1 (1.5)	1 (0.4)
Investigations	**0**	**0**	**0**	**1 (0.4)**	**1 (0.6)**	**1 (1.5)**	**2 (0.9)**
Neutrophil count decreased	0	0	0	0	0	1 (1.5)	1 (0.4)
Nervous system disorders	**1 (2.5)**	**3 (12.5)**	**4 (6.3)**	**4 (1.7)**	**4 (2.5)**	**1 (1.5)**	**5 (2.2)**
Cranial nerve paralysis	0	0	0	0	0	1 (1.5)	1 (0.4)
Dysarthria	0	0	0	0	0	1 (1.5)	1 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**0**	**0**	**0**	**0**	**2 (2.9)**	**2 (0.9)**
Malignant neoplasm of pleura	0	0	0	0	0	1 (1.5)	1 (0.4)
Tumour pain	0	0	0	0	0	1 (1.5)	1 (0.4)

Abbreviations: AE = adverse event; AI = aromatase inhibitor; ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in group; SOC = standard of care; TEAE = treatment-emergent adverse event.

[a] Identified as an AE in error, as disease progression should not be captured as an AE.

Note: MedDRA Version 23.0 was used. Subjects with 1 or more AEs within a system organ class of MedDRA were counted only once. System organ classes are sorted by descending order of frequency of preferred terms in the elacestrant group in Study 308. Preferred terms are sorted by descending order of frequency in the elacestrant group in Study 308 within each system organ class.

Taking into account the phase 1 studies, there was 1 case of grade 4 acute hepatic failure in study RAD1901-005, possibly related to elacestrant. In addition, there were two cases of treatment-related serious TEAEs pulmonary embolism (one in phase 1 study pool and one in study 308).

Serious adverse reactions reported in ≥ 1% of patients with elacestrant in the pooled safety set included nausea, dyspnoea, and thromboembolism (venous).

2.6.8.4. Laboratory findings

Shifts from NCI CTCAE Grade 0, 1, or 2 at baseline to any incidence of Grade 3 or 4 on treatment were infrequent, occurring in 7 subjects or less in any group for haematology variables, 5 subjects or less in any group for chemistry variables, and 2 subjects or less in any group for coagulation variables in Study 308.

High cholesterol (75.5% vs 58.5%), triglycerides (60.8% vs. 44.1%), creatinine (25.7% vs. 16.2%), and low bicarbonate (23.2% vs. 17.5%) were more common in the elacestrant group, whereas high alanine aminotransferase (ALT, 23.6% vs 16.5%), AST (33.2% vs. 28.3%), alkaline phosphatase (ALP, 24.9% vs 16.5%), and bilirubin (9.2% vs. 3.0%) were more common in the SOC group. Grade 3 or 4 abnormalities were rare in both groups. The only Grade 3 laboratory abnormality reported in ≥5% of subjects in any group was low lymphocytes (6.3% for elacestrant subjects and 3.9% for SOC subjects). No Grade 4 laboratory abnormalities were reported in ≥5% of subjects in any group.

No significant or clinically meaningful changes in clinical laboratory evaluations were observed in subjects treated with elacestrant.

Vital signs, physical findings, and other observations related to safety

No trends over time or differences between groups were observed in vital signs or blood pressure and no meaningful difference in abnormal vital signs was observed between elacestrant and the SOC in Study 308.

No significant or clinically meaningful changes in ECG parameters were observed in subjects treated with elacestrant in Study 308. Notably, there were no significant shifts in QT interval corrected with Fridericia's method (QTcF) during treatment with elacestrant. In Study 308, no subject had a change from baseline in QTcF that was > 60 msec. No TEAEs of bradycardia/sinus bradycardia or QTc prolongation were observed in the elacestrant group.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Intrinsic and extrinsic factors

Age: Most subjects (n=174) in the pooled phase 1 and phase 3 studies treated with elacestrant were <65 yrs of age; 127 subjects were ≥65 yrs and n=45 were ≥75 yrs. In general, no trends were observed for elacestrant (data not shown). In the RAD1901-308 study, 104 patients who received elacestrant were ≥ 65 years and 40 patients were ≥ 75 years. Gastrointestinal disorders were reported more frequently in patients aged ≥ 75 years.

Race: There were no differences in the overall safety profile between race (data not shown).

Hepatic impairment: Elacestrant is metabolised by the liver, and impaired hepatic function can increase risk for adverse reactions. AUCs of the moderate hepatic impairment group (n=10) were considerably higher (76% to 83%) than those of the normal hepatic function group, whereas exposure in subjects in the mild hepatic impairment group (n=10) was similar to that of the normal hepatic function group (Study RAD1901-117). Elacestrant has not been studied in patients with severe hepatic impairment, therefore no dose recommendation can be made for patients with severe hepatic impairment.

Patient with renal impairment: The renal excretion of elacestrant is reported to be minimal, therefore no renal impairment studies have been conducted. No dose adjustments are required in subjects with renal impairment.

Region: There were no notable differences in safety profile of elacestrant by region (data not shown).

Safety in relation to ESR1-mutation

The overall safety profile for elacestrant was comparable for ESR1-mut and ESR1-mut-nd subject groups. Further, no notable differences in common adverse events by PT were observed (data not shown).

2.6.8.7. Immunological events

Not applicable.

2.6.8.8. Safety related to drug-drug interactions and other interactions

Drug-drug interactions and other interactions are described in section 3.3.1.1 of the Overview. Briefly, elacestrant is primarily metabolised by cytochrome P450 (CYP)3A4 and is primarily eliminated in the liver via hepatic metabolism (CYP3A4) and biliary secretion. Therefore, elacestrant should not be co-administered with strong or moderate inhibitors of CYP3A4, which may increase the risk of adverse reactions, or strong or moderate inducers of CYP3A4, which may decrease elacestrant activity.

Elacestrant's relevance as a potential inhibitor of the efflux transporters P-glycoprotein and breast cancer resistance protein was evaluated in a clinical drug-drug interaction study (Study RAD1901-118). Elacestrant slightly increases digoxin exposure by 27% for Cmax and 13% for AUC. Elacestrant increases rosuvastatin exposure by 45% for Cmax and 23% for AUC.

2.6.8.9. Discontinuation due to adverse events

Overall, frequencies of TEAEs leading to discontinuation were low (6.3% elacestrant vs 4.4% SOC). For elacestrant, the most frequently reported TEAE by PT was nausea (1.3%) (

Table 74).

Table 74 Treatment-emergent adverse events leading to treatment discontinuation in ≥1% of subjects in any Study 308 group (Safety population)

System Organ Class Preferred Term[a]	Studies 005 and 106			Study 308			
					SOC		
	Elacestrant 400 mg Capsules (N = 40)	Elacestrant 400 mg Tablets (N = 24)	Elacestrant 400 mg Overall (N = 64)	Elacestrant 400 mg Tablets (N = 237)	Fulvestrant (N = 161)	AIs (N = 68)	SOC Total (N = 229)
Subjects with any TEAE leading to discontinuation of study drug	7 (17.5)	1 (4.2)	8 (12.5)	15 (6.3)	6 (3.7)	4 (5.9)	10 (4.4)
Gastrointestinal disorders	**5 (12.5)**	**1 (4.2)**	**6 (9.4)**	**4 (1.7)**	**0 (0.0)**	**1 (1.5)**	**1 (0.4)**
Nausea	3 (7.5)	0	3 (4.7)	3 (1.3)	0	0	0
Abdominal pain	0	0	0	1 (0.4)	0	1 (1.5)	1 (0.4)
Investigations	**0**	**0**	**0**	**2 (0.8)**	**3 (1.9)**	**1 (1.5)**	**4 (1.7)**
Aspartate aminotransferase increased	0	0	0	1 (0.4)	2 (1.2)	0	2 (0.9)
Alanine aminotransferase increased	0	0	0	0	2 (1.2)	0	2 (0.9)
Blood calcium increased	0	0	0	0	0	1 (1.5)	1 (0.4)
Blood and lymphatic system disorders	**1 (2.5)**	**0**	**1 (1.6)**	**0**	**0**	**1 (1.5)**	**1 (0.4)**
Lymphadenopathy	0	0	0	0	0	1 (1.5)	1 (0.4)
General disorders and administration site conditions	**2 (5.0)**	**0**	**2 (3.1)**	**2 (0.8)**	**0**	**1 (1.5)**	**1 (0.4)**
Gait disturbance	0	0	0	0	0	1 (1.5)	1 (0.4)
Infections and infestations	**0**	**0**	**0**	**0**	**0**	**1 (1.5)**	**1 (0.4)**
Pneumonia	0	0	0	0	0	1 (1.5)	1 (0.4)
Nervous system disorders	**0**	**0**	**0**	**2 (0.8)**	**1 (0.6)**	**1 (1.5)**	**2 (0.9)**
Cranial nerve paralysis	0	0	0	0	0	1 (1.5)	1 (0.4)
Dysarthria	0	0	0	0	0	1 (1.5)	1 (0.4)

Abbreviations: AE = adverse event; AI = aromatase inhibitor; ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in group; SOC = standard of care; TEAE = treatment-emergent adverse event.

[a] Preferred terms are summarized using AE synonym terms.

Note: MedDRA Version 23.0 was used. Subjects with 1 or more AEs within a system organ class of MedDRA were counted only once. System organ classes are sorted by descending order of frequency of preferred terms in the elacestrant group in Study 308. Preferred terms are sorted by descending order of frequency in the elacestrant group in Study 308 within each system organ class.

Dose interruptions and reductions

A total of 15.2% in the elacestrant arm had dose interruptions due to TEAEs. The most frequently reported TEAEs leading to dose interruptions were in the SOC of Gastrointestinal disorders (5.1%) and the most frequently reported GI TEAEs by PT were nausea (3.4%), abdominal pain upper and vomiting (each 1.3%). Dose interruptions were observed less frequently in the comparator arm (fulvestrant:3.1%, AI: 10.3%).

TEAEs leading to dose reduction occurred in 3.0% in the elacestrant arm and none in the comparator arm. The most frequently reported TEAEs leading to dose reductions were in the SOC of Gastrointestinal disorders (2.1%) and the most frequently reported GI TEAEs by PT was nausea (1.7%).

Update safety database DCO 8-Jul-2022

The applicant submitted an update of the safety database with longer follow-up of study 308 (additional 10 months) based on the new DCO of 8-Jul-2022 (initial DCO: 06 September 2021). Further, one additional patient was identified that was treated with fulvestrant (adding up to n=230) and included in the updated safety set. A total of 8/237 and 3/230 patients were continuing treatment with elacestrant and SOC, respectively. A the initial DCO, most patients already discontinued treatment (18/237 and 6/229 patients continued treatment with elacestrant and SOC, respectively).

With the safety update, median exposure time for study 308 remained the same but the maximum time on treatment increased, for elacestrant maximum exposure increased from 756 to 978 days.

Within study 308, 51 patients on elacestrant had a treatment duration of 6 months or longer, and 25 patients had a treatment duration of 12 months or longer.

An updated summary of TEAEs for the safety population and for ESR1-mut patients is shown below. Frequencies of TEAEs were comparable to that of the initial DCO. There were no clinically relevant changes or new safety signals based on the updated safety database.

Table 75 Overview of TEAEs (Safety population) -Update DCO 08-Jul-2022

	Studies 005 and 106				Study 308			
	Elacestrant 400 mg Capsules (N = 40)	Elacestrant 400 mg Tablets (N = 24)	Elacestrant 400 mg Overall (N = 64)		Elacestrant 400 mg Tablets (N = 237)	SOC		
						Fulvestrant (N = 162)	AIs (N = 68)	SOC Total (N = 230)
Number of subjects with at least 1 TEAE	39 (97.5)	22 (91.7)	61 (95.3)		218 (92.0)	145 (89.5)	53 (77.9)	198 (86.1)
Any treatment-related TEAEs	37 (92.5)	19 (79.2)	56 (87.5)		150 (63.3)	72 (44.4)	28 (41.2)	100 (43.5)
Any NCI CTCAE Grade 3 and Grade 4 TEAEs	15 (37.5)	10 (41.7)	25 (39.1)		64 (27.0)	35 (21.6)	14 (20.6)	49 (21.3)
Any treatment-related NCI CTCAE Grade 3 and Grade 4 TEAEs	8 (20.0)	1 (4.2)	9 (14.1)		17 (7.2)	5 (3.1)	2 (2.9)	7 (3.0)
Any fatal (Grade 5) TEAEs	1 (2.5)	1 (4.2)	2 (3.1)		4 (1.7)	5 (3.1)	1 (1.5)	6 (2.6)
Any treatment-related fatal (Grade 5) TEAEs	0	0	0		0	0	0	0
Any serious TEAEs	7 (17.5)	8 (33.3)	15 (23.4)		29 (12.2)	15 (9.3)	10 (14.7)	25 (10.9)
Any treatment-related serious TEAEs	1 (2.5)	1 (4.2)	2 (3.1)		3 (1.3)	0	0	0
Any TEAEs leading to dose interruption	12 (30.0)	8 (33.3)	20 (31.3)		36 (15.2)	5 (3.1)	7 (10.3)	12 (5.2)
Any treatment-related TEAEs leading to dose interruption	8 (20.0)	1 (4.2)	9 (14.1)		16 (6.8)	0	4 (5.9)	4 (1.7)
Any TEAEs leading to dose reduction	0	0	0		7 (3.0)	0	NA	0
Any treatment-related TEAEs leading to dose reduction	0	0	0		6 (2.5)	0	NA	0
Any TEAEs leading to discontinuation of study drug	7 (17.5)	1 (4.2)	8 (12.5)		15 (6.3)	6 (3.7)	4 (5.9)	10 (4.3)
Any treatment-related TEAEs leading to discontinuation of study drug	6 (15.0)	0	6 (9.4)		8 (3.4)	1 (0.6)	1 (1.5)	2 (0.9)

Abbreviations: AI = aromatase inhibitor; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic case report form; ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in group; NA = not applicable; NCI = National Cancer Institute; SOC = standard of care; TEAE = treatment-emergent adverse event.

Note: MedDRA Version 23.0 was used; NCI CTCAE Version 4.3 was used for Studies 005 and 106, and NCI CTCAE Version 5.0 was used for Study 308. If a subject experienced more than 1 event in a given category, that subject was counted only once in that category. A TEAE was considered treatment-related if its causality was "possibly related," "definitely related," or "related" on the AE eCRF pages from each study.

Table 76 Overview of TEAEs (ESR1-mut subjecs in Study 308 Safety population) – Update DCO 08-Jul-2022

	Elacestrant 400 mg Tablets (N = 115)	SOC		
		Fulvestrant (N = 79)	AIs (N = 27)	SOC Total (N = 106)
Number of subjects with at least 1 TEAE	105 (91.3)	71 (89.9)	21 (77.8)	92 (86.8)
Any treatment-related TEAEs	71 (61.7)	40 (50.6)	9 (33.3)	49 (46.2)
Any CTCAE Grade 3 and Grade 4 TEAEs	32 (27.8)	17 (21.5)	6 (22.2)	23 (21.7)
Any treatment-related CTCAE Grade 3 and Grade 4 TEAEs	10 (8.7)	4 (5.1)	1 (3.7)	5 (4.7)
Any fatal (Grade 5) TEAEs	3 (2.6)	1 (1.3)	0	1 (0.9)
Any serious TEAEs	14 (12.2)	7 (8.9)	5 (18.5)	12 (11.3)
Any treatment-related serious TEAEs	2 (1.7)	0	0	0
Any TEAEs leading to dose interruption	25 (21.7)	2 (2.5)	5 (18.5)	7 (6.6)
Any treatment-related TEAEs leading to dose interruption	10 (8.7)	0	3 (11.1)	3 (2.8)
Any TEAEs leading to dose reduction	6 (5.2)	0	NA	0
Any treatment-related TEAEs leading to dose reduction	5 (4.3)	0	NA	0
Any TEAEs leading to discontinuation of study drug	6 (5.2)	3 (3.8)	1 (3.7)	4 (3.8)
Any treatment-related TEAEs leading to discontinuation of study drug	5 (4.3)	1 (1.3)	1 (3.7)	2 (1.9)

Abbreviations: AI = aromatase inhibitor; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic case report form; *ESR1* = estrogen receptor 1 gene; *ESR1*-mut = *ESR1* mutation; N = total number of subjects in group; SOC = standard of care; TEAE = treatment-emergent adverse event.

Note: Events were coded using MedDRA version 23.0 and CTCAE version 5.0. If a subject experienced more than 1 event in a given category, that subject is counted only once in that category. A TEAE was considered treatment-related if its causality was "possibly related," "definitely related," or "related" on the AE eCRF pages from each study

Primary causes of death within 30 days and 100 days of last dose of study treatment are shown below.

Table 77 Main reason for death within 30 days since last dose

	Cause of Death	N (%)
Elacestrant	Adverse Event	3 (2.5 %)
	Breast Cancer	2 (1.7 %)
SOC	Adverse Event	4 (3.6 %)
	Breast Cancer	2 (1.8 %)

Abbreviations: SOC = Standard of Care.

Percentages are calculated over the total number of death patients for each study treatment in the ITT population. Elacestrant: n= 119, SOC: n= 111.

Adverse events reported causing death. Elacestrant: Antiphospholipid syndrome, Cardiac arrest, Septic shock; SOC: Arrhythmia, COVID-19, Gastric perforation, Pneumonia. None of these AEs were considered related to trial theapy by the inviestigator.

Data cut-off: 08 July 2022.

Table 78 Primary reason for death within 100 days since last dose

	Cause of Death	N (%)
Elacestrant	Adverse Event	4 (3.4 %)
	Breast Cancer	9 (7.6 %)
	Other[a]	1 (0.8 %)
SOC	Adverse Event	6 (5.4 %)
	Breast Cancer	18 (16.2 %)
	Not specified	1 (0.9 %)
	Other	3 (2.7 %)
	Unknown	2 (1.8 %)

Abbreviations: SOC = Standard of Care.
a. This subject died due to a gallbladder attack ("other" reason); the latter occurred > 30 days after the last dose.
Percentages are calculated over the total number of death patients for each study treatment in the ITT population. Elacestrant: n= 119, SOC: n= 111.
Adverse events reported causing death. Elacestrant: Antiphospholipid syndrome, Cardiac arrest, Diverticulitis, Septic shock. SOC: Arrhythmia, COVID-19, Gastric perforation, Ischaemic stroke, Myocardial infarction, Pneumonia.
Other reasons reported include complications and disease progression,
Data cut-off: 08 July 2022.

Selected adverse reaction

Regarding the timing and management of nausea, the median time to the subjects first TEAE of PT nausea was 14 days (range: 1 to 490 days) vs. 27 days (range: 1 to 225 days) in the elacestrant and SOC arm, respectively. From Cycle 2 onward in both arms, the incidence of TEAEs of PT nausea the frequency was generally lower in subsequent Cycles. A total of 12 (5%) subjects in the elacestrant arm and 13 (5.4%) subjects in the SOC arm received prophylactic treatment for nausea, whereas 28 (11.8%) subjects and 16 (7%) subjects received an antiemetic for nausea.

An overview of TEAEs by age group is shown below.

Table 79 Overview of treatment-emergent adverse events by age group (Safety population, elacestrant arm, n=237)

MedDRA Terms	Age< 65 (N = 134)	Age 65 - 74 (N = 63)	Age 75 - 84 (N = 38)	Age 85+ (N = 2)	Overall (N = 237)
Total AEs	122 (91%)	57 (90.5%)	37 (97.4%)	2 (100%)	218 (92%)
Serious AEs - Total	16 (11.9%)	10 (15.9%)	3 (7.9%)	0 (0.0%)	29 (12.2%)
- Fatal	1 (0.7%)	3 (4.8%)	0 (0.0%)	0 (0.0%)	4 (1.7%)
- Hospitalization / Prolong Existing Hospitalization	16 (11.9%)	10 (15.9%)	3 (7.9%)	0 (0.0%)	29 (12.2%)
- Life-Threatening	0 (0.0%)	2 (3.2%)	0 (0.0%)	0 (0.0%)	2 (0.8%)
- Disability/Incapacity	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
- Other (Medically Significant)	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
AE leading to Drop-Out	11 (8.2%)	3 (4.8%)	1 (2.6%)	0 (0.0%)	15 (6.3%)
Psychiatric Disorders	22 (16.4%)	6 (9.5%)	6 (15.8%)	0 (0%)	34 (14.3%)
Nervous System Disorders	32 (23.9%)	13 (20.6%)	10 (26.3%)	0 (0%)	55 (23.2%)
Injury, Poisoning And Procedural Complications	4 (3%)	7 (11.1%)	2 (5.3%)	0 (0%)	13 (5.5%)
Cardiac Disorders	6 (4.5%)	1 (1.6%)	2 (5.3%)	0 (0%)	9 (3.8%)
Vascular Disorders	22 (16.4%)	11 (17.5%)	9 (23.7%)	1 (50%)	43 (18.1%)
Central Nervous System Haemorrhages and Cerebrovascular Accidents	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Infections And Infestations	25 (18.7%)	13 (20.6%)	5 (13.2%)	0 (0%)	43 (18.1%)
Anticholinergic syndrome	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Quality of Life decreased [1]	7 (5.2%)	5 (7.9%)	5 (13.2%)	0 (0%)	17 (7.2%)
Sum of postural hypotension, falls, blackouts, syncope, dizziness, ataxia, fractures [2]	9 (6.7%)	7 (11.1%)	5 (13.2%)	0 (0.0%)	21 (8.9%)
Gastrointestinal Disorders	89 (66.4%)	33 (52.4%)	31 (81.6%)	2 (100%)	155 (65.4%)
Musculoskeletal And Connective Tissue Disorders	64 (47.8%)	20 (31.7%)	20 (52.6%)	2 (100%)	106 (44.7%)
General Disorders And Administration Site Conditions	51 (38.1%)	22 (34.9%)	15 (39.5%)	1 (50%)	89 (37.6%)

[1] Note 1: Absolute Difference in EQ5D02-EQ VAS Score between Baseline and "Cycle 6 - Day 1" Visit was calculated.
[1] Note 2: An absolute difference <-7 was considered as a QoL decrease. Overall number of patients with missing values (i.e. no baseline and/or cycle 6 data available) amounts to 173 units.
[1] Note 3: Source "https://hqlo.biomedcentral.com/articles/10.1186/1477-7525-5-70"
[2] Adverse Events (PT Term) included: Dizziness, Fall, Femoral neck fracture, Hand fracture, Hypotension, Pathological fracture, Rib fracture, Syncope

2.6.8.10. Post marketing experience

Not applicable.

2.6.9. Discussion on clinical safety

The total safety database for elacestrant in the proposed target population and at the proposed dose consists of 301 subjects, of which 237 were treated in the pivotal phase 3 study 308. At data cut-off (DCO) of 06 September 2021, the median duration on treatment was 84 days for study 308 and somewhat longer for the pooled phase 1 studies (median of 117 days). A safety update was provided with the DCO 8-Jul-2022. Median exposure time for study 308 remained the same as most patients already had discontinued treatment at the time of initial DCO, however the maximum time on elacestrant treatment increased from 756 to 978 days. Long-term safety data is limited (n=51 ≥6 months and n=25 ≥12 months in study 308). Despite these limitations, the safety database can be considered acceptable given the known mechanism of action, the well-established safety profile of and long-term experience with fulvestrant, and available non-clinical data that did not reveal major issues. Routinely review of long-term safety as part of future PSURs is considered sufficient.

The relative dose intensity being >90% indicates that most subjects tolerated the proposed starting dose of 400 mg. The frequency of subjects with TEAEs leading to discontinuation was low and in the same order of magnitude as the SOC (6.3% vs. 4.4% SOC). Although dose reductions and dose interruptions were more common with elacestrant (3.0% vs 0% SOC and 15.2% vs. 5.2% SOC, respectively), overall frequencies are acceptable and support the recommended dose. Some uncertainty remains on the impact of the reduced dose on efficacy, given the limited dose-finding data (see discussion on clinical efficacy). However, it is reassuring that few patients needed dose reductions (n=6 in the ESR1-mut group). Available limited data on efficacy do not suggest inferior clinical outcome for patients with one dose reduction. However, there are no data for patients with a second dose reduction due to adverse events. Data suggest a lower target engagement and undertreatment cannot be ruled out. Therefore, this second dose reduction step is not supported by data and was not approved. A quarter of subjects on elacestrant experienced Grade ≥3 TEAEs, which was slightly higher than for the SOC (27.0% vs. 20.0%). The most common Grade ≥3 (≥2%) adverse reactions of elacestrant were nausea (2.7%), AST increased (2.7%), ALT increased (2.3%), anaemia (2%), back pain (2%), and bone pain (2%). Treatment-related AEs were observed more frequently compared to the SOC (63.3% vs. 43.7%), however, most were mild or moderate.

The most frequently reported TEAEs (≥10%) for elacestrant per PT were nausea, vomiting, and fatigue. Other commonly (≥10%) observed adverse events with elacestrant were triglycerides increased, cholesterol increased, calcium decreased, creatine increased, sodium decreased, potassium decreased, decreased appetite, back pain, arthralgia, diarrhoea, alanine aminotransferase increased (ALT), aspartate aminotransferase increased (AST), constipation, headache, hot flush, abdominal pain, anaemia and dyspepsia.

Gastrointestinal events were the most frequently reported TEAEs with elacestrant (65.4% vs. 34.1% SOC), and the most common individual TEAEs were nausea (35.0% vs. 18.8% SOC), vomiting (19.0% vs. 8.3% SOC) and diarrhoea (13.9% vs. 10.0% SOC). Higher frequencies as compared to fulvestrant may in part be due to the different route of administration. Gastro-intestinal (GI) events were also the most frequently reported treatment-related TEAEs with elacestrant, especially nausea (25.3%) and vomiting (11.0%). However, these were seldom of high grade (Grade 3 or 4 nausea: 1.7%). GI events and especially nausea were also the most frequently reported TEAEs leading to dose modifications. However, few subjects (1.3%) discontinued elacestrant treatment due to nausea (1.3%). Most events occurred during the first treatment cycle. Approximately 5% of patients received prophylactic

treatment for nausea in both treatment arms and a somewhat higher % of patients on elacestrant received anti-emetics compared to the SOC (11.8% vs. 7%). The higher frequency of treatment-related AEs compared to the SOC was mainly due to a difference in GI events. Elacestrant should be administered with food as in the clinical study and administration with food may improve gastrointestinal tolerability (see 2.6.2.). Gastrointestinal events like nausea, vomiting and dyspepsia were reported more frequently with the capsules compared to the tablet formulation, the reason for this is not clear as PK was comparable. Of note, if the patient vomits after taking the Orserdu dose, the patient should not take an additional dose on that day and should resume the usual dosing schedule the next day at the usual time. Other frequently reported TEAEs with elacestrant were fatigue (19.0%) and arthralgia (14.3%), which are known for endocrine therapies (ET) and observed at comparable frequencies as for the SOC (<5% difference). This also holds true for known events like elevated hepatic enzymes and hot flushes. Most of these events were also mild or moderate. Most commonly reported Grade 3 or 4 TEAEs with elacestrant were nausea, back pain, bone pain (2.5% each), alanine aminotransferase increased, and blood pressure increased (2.1% each). Most commonly reported Grade 3 or 4 TEAEs with fulvestrant were blood pressure increased (2.5%) and anaemia (1.2%). For AI, most commonly reported Grade 3 or 4 TEAEs were nausea, abdominal pain, blood pressure increased, gamma-glutamyltransferase increased, neutropenia, and tumour pain (2.9% each). TEAEs for the SOC were in line with those known and reported in the SmPC and no new signals were identified. Injection site pain was reported in 8.7% of subjects treated with fulvestrant. TEAEs in the SOC Musculoskeletal disorders and connective tissue were more often reported as treatment-related for the comparator arm (17.9% vs. 7.6%).

The frequency of subjects experiencing a SAE was comparable between elacestrant and the SOC (12.2% vs. 10.9% SOC) and TEAEs by PT occurred in general in single cases. The only reported SAEs by PT occurring in more than one subject for elacestrant was nausea (n=3). Treatment-related SAEs were few (1.3%) and only reported in the elacestrant arm. Based on OS data, 29.3% and 33.2% of subjects died in the elacestrant and SOC arm, respectively. There were only few TEAEs (1.7% vs. 2.6% SOC) with an outcome of death, occurring in single cases and none of these were considered related to elacestrant. Based on the safety update, 2.5% and 3.4% of patients died due to an AE within 30 days and 100 days since the last dose of elacestrant, respectively. None was assessed as treatment-related by the investigator and no clinically meaningful differences were observed compared to the SOC. The narratives for the patients who died from other causes than PD in the pivotal study as assessed are agreed.

Shifts from low grade to high grade in laboratory levels were low and did not identify new safety issues. Although high cholesterol (75.5% vs. 58.5% SOC) and high triglyceride levels (60.8% vs. 44.1%) were observed more frequently with elacestrant, grade 3 or 4 levels were low (maximum about 2%) and few patients had shifts from low to high grade which is reassuring. In addition, there were no signals of increased cardiovascular toxicity with elacestrant based on preclinical or clinical data, though follow-up time in the clinical study was limited. No TEAEs of bradycardia/sinus bradycardia or QTc prolongation were observed in the elacestrant group, supported by the lack of a signal for QTc prolongation with elacestrant up to a 2.5 times higher dose. However, data at the higher end were limited. Fulvestrant has not been associated with significant cardiotoxicity based on long-term experience.

In general, no clinically meaningful vital sign results were observed in patients in either treatment arm.

Adverse reactions leading to discontinuation in ≥ 1% of patients included nausea and decreased appetite. Adverse reactions leading to dose interruption in ≥ 1% of patients were nausea, abdominal pain, alanine aminotransferase increased, vomiting, rash, bone pain, decreased appetite, aspartate aminotransferase increased, and diarrhoea.

There were no notable differences in safety profile for age, however the number of subjects ≥75 years was low (n=45). There were no clear trends for an increase in specific AEs except for gastrointestinal events. This was also seen for the SOC. The SmPC appropriately states that data in elderly (≥75 years) are limited (SmPC section 4.2 and 4.8). No differences were observed in safety in relation to race or region, however, almost all patients were caucasians. On the other hand, no differences are expected based on the mechanism of action or are known for fulvestrant. Race was not formally assessed as a covariate in the population pharmacokinetics due to the limited number of non-caucasian subjects included in the clinical development. Despite these limitations, an exploratory analysis based on PK data from Phase 1 and Phase 3 studies used for the popPK model development, did not suggest significant differences in exposure among different races.

As elacestrant is metabolised by the liver, impaired hepatic impairment can increase risk of adverse reactions. PK data showed that, in contrast to subjects with mild hepatic impairment, subjects with moderate or severe hepatic impairment had increased elacestrant exposure. Based on these PK data elacestrant dose should be reduced to 300 and 200 mg QD in patients with moderate hepatic impairment. Elacestrant has not been studied in patients with severe hepatic impairment, therefore no dose recommendation can be made for patients with severe hepatic impairment (see SmPC section 4.2). A warning is included in section 4.4 of the SmPC stating that elacestrant is metabolised by the liver, and impaired hepatic function can increase the risk for adverse reactions. Therefore, Orserdu should be used cautiously in patients with hepatic impairment and patients should be regularly and closely monitored for adverse reactions. Administration of elacestrant should be undertaken with caution at a dose of 258 mg once daily in patients with moderate hepatic impairment (see SmPC section 4.2). In the absence of clinical data, elacestrant is not recommended in patients with severe hepatic impairment (Child-Pugh C) (see SmPC section 4.2). Further data will be obtained post marketing (see 2.6.2.). As elacestrant is primarily metabolised by cytochrome P450 (CYP)3A4, co-administration with moderate to strong CYP3A4 inducers or inhibitors affects elacestrant exposure and concomitant use with strong and moderate inhibitors/inducers should be avoided (see SmPc sections 4.2 and 4.4).

As thromboembolic events are commonly observed in patients with advanced breast cancer and have been observed in clinical studies with elacestrant, this should be taken into consideration when prescribing elacestrant to patients at risk (See SmPC sections 4.4 and 4.8).

Based on the mechanism of action of elacestrant and findings from reproductive toxicity studies in animals (see 2.5.4.5.), elacestrant can cause foetal harm when administered to pregnant women (see section 2.5.4.5. and SmPC section 4.6). Given the extended knowledge on the safety of fulvestrant, the current provided information and warnings in the SmPC, and in line with the RMP of fulvestrant, the risk of embryo-foetal toxicity in the off-label setting (premenopausal women) has not been included as safety concern in Orserdu RMP (see 2.7.). The topic will be followed as part of routine pharmacovigilance activity of PSURs. Orserdu has no or negligible influence on the ability to drive and use machines. Since fatigue, asthenia, and insomnia have been reported in some patients taking elacestrant (see 2.6.8.2.), caution should be observed by patients who experience those adverse reactions when driving or operating machinery.

In general, the overall safety profile for elacestrant was comparable for ESR1-mut and ESR1-mut-nd (nd=not detected) subject groups. No notable differences in common adverse events by PT were observed, nor are to be expected based on the mechanism of action. The selection of the non-restricted population as the basis for the safety information in the SmPC is acceptable as it allows a more precise estimation of frequencies of ADRs. From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics. A dose reduction is recommended for patients with adverse reactions to 258mg once daily (3 tables of 86mg) based on severity grade of adverse reactions. When occurrence of Grade 2 adverse reactions,

interruption of Orserdu should be considered until recovery to Grade ≤ 1 or baseline. Then treatment with Orserdu can be resumed at the same dose level. For Grade 3, treatment with Orserdu should be interrupted until recovery to Grade ≤ 1 or baseline. The dose should be reduced to 258 mg when resuming therapy. If the Grade 3 toxicity recurs, Orserdu treatment should be interrupted until recovery to Grade ≤ 1 or baseline. The reduced dose of 258 mg may be resumed if at the discretion of the treating physician if the patient is benefiting from treatment. If a Grade 3 or intolerable adverse reaction recurs, Orserdu should be permanently discontinued. For Grade 4, treatment with Orserdu should be interrupted until recovery to Grade ≤ 1 or baseline. The dose should be reduced to 258 mg when resuming therapy. If a Grade 4 or intolerable adverse reaction recurs, Orserdu should be permanently discontinued.

The maximum recommended daily dose of ORSERDU is 345 mg. The highest dose of ORSERDU administered in clinical studies was 1000 mg per day. The adverse drug reactions reported in association with doses higher than the recommended dose were consistent with the established safety profile (see SmPC sections 4.8 and 4.9). The frequency and severity of gastrointestinal disorders (abdominal pain, nausea, dyspepsia and vomiting) appeared to be dose-related. There is no known antidote for an overdose of elacestrant. Patients should be closely monitored and treatment of overdose should consist of supportive treatment.

2.6.10. Conclusions on the clinical safety

The safety profile of the oral SERD elacestrant in the proposed target population resembles that known for endocrine therapies, however frequencies of gastrointestinal events like nausea and vomiting were markedly increased. No new safety issues were identified. Treatment-related TEAEs were more frequently observed compared to the SOC, mainly due to an increase in gastrointestinal events such as nausea and vomiting. Most events were mild or moderate and dose reductions or discontinuations were observed in a low portion of subjects, indicating acceptable tolerability of the recommended dose with supportive measures. Long-term safety information on elacestrant is limited, however this is not of major concern due to the long-standing experience with fulvestrant which is a similar drug-in-class. Elacestrant offers the convenience of the oral route of administration compared to the IM administration of fulvestrant at the cost of milder to moderate GI events.

The safety profile is overall acceptable and clinically manageable.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns

Table 80: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

2.7.2. Pharmacovigilance plan

Based on clinical safety data, there are no additional pharmacovigilance activities warranted beyond routine activities (e.g. adverse reactions reporting and signal detection).

2.7.3. Risk minimisation measures

None.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 28.12.2022. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Orserdu (elacestrant) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

In this MAA, the applicant claimed the following therapeutic indication:

Orserdu is indicated for the treatment of postmenopausal woman, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced or metastatic breast cancer who have progressed following at least one line of endocrine therapy.

The recommended indication reflecting the data evaluated is:

"Orserdu monotherapy is indicated for the treatment of postmenopausal women, and men, with estrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK4/6 inhibitor."

3.1.2. Available therapies and unmet medical need

The standard-of-care first-line therapy for patients with oestrogen receptor-positive (ER+), HER2-negative metastatic breast cancer (mBC) is CDK4/6 inhibitor (CDK4/6i) in combination with endocrine therapy. After progression on CDK4/6i, the optimal sequence of endocrine-based therapy is uncertain, underlining an unmet medical need. The choice of next-line treatment is dependent on which agents were used previously, duration of response to previous endocrine therapy, disease burden, patient preference and treatment availability. According to ESMO Guidelines, evidence-based available options for second-line therapy are fulvestrant-alpelisib (for *PIK3CA* mutated tumours), exemestane-everolimus, tamoxifen-everolimus, fulvestrant-everolimus, aromatase inhibitor (AI), tamoxifen, fulvestrant, chemotherapy or PARP inhibitors for tumours harbouring genomic *BRCA* mutations. At least two lines of endocrine-based therapy are preferred before moving to chemotherapy (Gennari et al, *Annals of Oncology*, 2021).

3.1.3. Main clinical studies

The application is based on the pivotal Study 308, a phase 3, multicentre, randomised, open-label, active-controlled study of elacestrant versus standard of care (SOC) therapy (fulvestrant or AI) in postmenopausal women and men with oestrogen receptor (ER)+/HER2- mBC whose disease has relapsed or progressed on at least 1 and no more than 2 prior lines of endocrine therapy for mBC. In total 478 patients were randomised 1:1 to elacestrant or SOC. Randomisation was stratified by *ESR1* mutational status, prior fulvestrant, and visceral metastases. The studied dose of elacestrant was 400 mg[2] once daily.

[2] As elacestrant dihydrochloride salt, corresponding to 345mg elacestrant

3.2. Favourable effects

The presented data are from the final analysis for superiority of the primary efficacy endpoints of blinded imaging review committee (IRC)-assessed progression-free survival (PFS) in *ESR1*-mut patients or in all patients (*ESR1*-mut + *ESR1*-mut-nd (not detected)) at data cut-off date 06 September 2021. As the higher p-value was <0.0475, the study met both primary endpoints. Results for OS are from the final OS analysis with data cut-off 2nd September 2022.

- **Primary endpoint: IRC-Assessed PFS**
  - **Overall population (n=478)**- Median PFS was 2.79 months (95%CI: 1.94-3.78) in the elacestrant arm versus 1.91 months (95%CI: 1.87-2.10) in the SOC arm, hazard ratio 0.70 (95%CI: 0.55-0.88), p=0.0018
  - ***ESR1*-mut population (n=228)**- Median PFS was 3.78 months (95%CI: 2.17-7.26) in the elacestrant arm versus 1.87 months (95%CI: 1.87-2.14) in the SOC arm, hazard ratio 0.55 (95%CI: 0.39-0.77), p=0.0005i
- **Key secondary endpoint: Overall survival (OS)**- The key secondary endpoint OS was not statistically different between the elacestrant and SOC arms in both the overall and *ESR1*-mut population and the KM curves did not show signals of a detriment. In the *ESR1*-mut population, median OS was 24.18 months (95%CI: 20.53-28.71) in the elacestrant arm and 23.49 months (95%CI:15.64-29.90) in the SOC arm.
- **Secondary endpoint: IRC-assessed PFS in *ESR1*-mut-nd population**- Median PFS was 1.94 months (95%CI: 1.87-3.55) in the elacestrant arm versus 1.97 months (95%CI: 1.87-2.20) in the SOC arm, hazard ratio 0.86 (95%CI: 0.63-1.19), p=0.3082
- **Secondary endpoint: Investigator-assessed PFS**- Median PFS per investigator was 2.17 months (95%CI: 1.94-3.58) in the elacestrant arm versus 2.00 months (95%CI: 1.87-2.14) in the SOC arm, hazard ratio 0.77 (95%CI: 0.63-0.95), p=0.0097 in the overall population. In the *ESR1*-mut population, median PFS per investigator was 3.65 months (95%CI: 2.10-5.36) in the elacestrant arm versus 2.07 months (95%CI: 1.87-3.48) in the SOC arm, hazard ratio 0.65 (95%CI: 0.48-0.88), p=0.0049.

Updated PFS (with 7 additional PFS events) and OS analyses from a data cut-off of 02 September 2022 showed similar results.

3.3. Uncertainties and limitations about favourable effects

Major changes occurred in the efficacy testing procedures for PFS and OS analyses. Separation of PFS KM curves can only be ascertained at and after 8 weeks due to a stark drop in the curves at the first tumour assessment and the curves are uncertain after 8 months. The differences in PFS were only observed at and after the first scan at 8 weeks, but tipping point analyses correcting for early censoring, showed that in the *ESR1*-mut population the results are robust.

Discordance in PFS events was observed between the independent and investigator review leading to possible informative censoring and potential bias in the IRC-assessed PFS in favour of the elacestrant arm.

Final OS results were presented with a high number of censored observations. The key secondary endpoint OS was not statistically different between the elacestrant and SOC arms in both the overall and *ESR1*-mut population, though reassuringly the KM curves did not show signals of a detriment.

The recommended dose of 400 mg once daily (QD) in Study 308 was based on Study 005 and Study 106. The rationale for the posology of 400 mg QD was not sufficiently supported and the optimal dose of elacestrant was considered uncertain (See 2.6.6.). Results from the pharmacodynamic **Study 106** showed that both doses of 400 mg and 200 mg reduced FES uptake in tumour lesions at day 14, although less reduction was observed with the 200 mg dose (see 2.6.2.2.). It is acknowledged that the B/R assessment should be made based on the posology of 400 mg QD used in the pivotal study.

Test for ESR1 mutational status (i.e. Guardant360):

- While certain specific ESR1 mutations (e.g., D538G, Y537S, Y537N) are most common, ESR1 mutations can be highly diverse. The scientific rationale to define patients with 'any ESR1 mutation in the ligand binding domain (i.e. any mutation between codons 310 and 547)' as ESR1 mutation positive ('ESR1-mut') – being supported by preclinical data – can be followed. However, a sound validation of this definition of ESR1 mutation positivity (i.e. biomarker positivity) is not possible due to the diversity and rarity of single ESR1 mutations within the ligand binding domain.
- *Clinical validation*: The explorative analysis by mutation and the analysis of pooled rare mutations do not contradict the assumption of a homogeneous effect across mutations. However, the limitations of these analyses, such as not all mutations being represented in the study, small sample sizes and median alone not describing treatment effects comprehensively, mean that no definite conclusion on consistency of effects across mutations is possible based on the clinical data.

Cut-point selection: It remains unclear whether the threshold applied in study RAD1901-308 (EMERALD) was optimal or whether a lower or higher threshold defining patients as 'ESR1-mutant' would lead to a better benefit-risk ratio.

3.4. Unfavourable effects

Almost all of the patients experienced at least one adverse event (AE) in the pivotal study 308 and most of these were treatment-related. Most AEs were also grade 1 or 2. Treatment-related AEs (ADRs) with elacestrant were also nausea (25.3%), vomiting (11.0%), and fatigue (11.0%). Additional back pain (13.9%), aspartate aminotransferase increased (13.1%), and hot flushes (11.4%), were commonly observed events and are known AEs for ET. Gastrointestinal toxicity was markedly increased with elacestrant vs SOC, especially nausea (35.0% vs 18.8%), vomiting (19.0% vs. 8.3%), constipation (12.2% vs. 6.6%), and dyspepsia (10.1% vs. 2.6%). Other AEs known for ET like fatigue/asthenia, elevated hepatic enzymes, hot flushes and musculoskeletal and joint pain were observed at the same order of magnitude as for the SOC.

Grade 3 or 4 AEs were observed more frequently with elacestrant compared to the SOC (27.0% vs. 20.5%). Most frequently observed grade 3 or 4 AEs in study 308 were nausea, back pain, and bone pain (2.5% each). Nausea was the only treatment-related grade ≥3 events observed in more than 1% of the subjects treated with elacestrant.

Overall, 29.3% of the patients had died in the elacestrant arm, most commonly due to disease progression and rarely due to an adverse event (1.7%). The causality assessment in the narratives for the patients who died from other causes than PD in the pivotal study are agreed.

Serious adverse events (SAEs) were observed in 12.2% of subjects, comparable to the SOC. Nausea was the only SAE occurring in more than one subject (1.3%).

The overall discontinuation rate due to AEs in study 308 was 6.3%, and the most common AE leading to discontinuation was nausea (1.3%). Dose modifications (interruptions or reductions) were more commonly observed compared to the SOC, mostly dose interruptions due to GI events whereas dose reductions occurred less frequently (3.0%).

The safety profile was comparable independent of *ESR1*-mutation.

3.5. Uncertainties and limitations about unfavourable effects

The rationale for the posology of 400 mg QD is not sufficiently supported and the optimal dose of elacestrant is uncertain. However, the B/R assessment was made based on the posology of 400 mg QD used in the pivotal study and based on efficacy and safety results drawn from the pivotal clinical trial.

Elacestrant is metabolised by the liver. No clinical data is available in patients with severe hepatic impairment. Further data will be obtained post-marketing from a PK study in order to provide dose recommendations for this population.

Safety data in elderly (≥75 yrs) is limited (n=45). Appropriate statements are included in the SmPC (section 4.2 and 4.8).

The total safety database is limited with a total of 301 subjects with metastatic breast cancer and especially limited long-term safety information in the target population.

However, given the long-term experience with fulvestrant, routinely review of long-term safety of elacestrant as part of future PSURs is considered sufficient.

3.6. Effects Table

Table 81: Effects Table for Orserdu or the treatment of postmenopausal woman, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced or metastatic breast cancer who have progressed following at least one line of endocrine therapy (data cut-off 06 September 2021 for all analyses except for final OS analysis with data cut-off 02 September 2022).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
PFS *ESR1*-mut population	Progression-free survival	Median in months (95%CI)	3.8 (2.2-7.3)	1.9 (1.9-2.1)	**Strengths**: RCT vs SOC, independent review **Uncertainties**: Changes in analysis plan, discordance investigator assessment	CSR
OS *ESR1*-mut population	Overall survival	Median in months (95%CI)	24.2 (20.5-28.7)	23.5 (15.6-29.9)	**Strengths**: RCT vs SOC **Uncertainties**: Immature	CSR
Unfavourable Effects						

Grade 3 or 4 AEs	Incidence of Grade 3 or 4 events	%	27.0	20.5	**Strengths**: RCT vs SOC	CSR
SAEs	Incidence of SAEs	%	12.2	10.9		CSR
AEs leading to discontinuations	Incidence of AEs leading to drug discontinuation	%	6.3	4.4		CSR
GI events	Incidence of GI events	%	65.4	34.1		CSR
Nausea	Incidence of nausea	%	35.0	18.8	Most events were grade 1 or 2 and seldomly led to discontinuation	CSR
Vomiting	Incidence of vomiting	%	19.0	8.3		CSR

Abbreviations: CI confidence interval, HR hazard ratio, NC not calculable, OS overall survival, PFS progression-free survival, RCT randomised controlled trial, SOC standard of care

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The primary IRC-assessed PFS showed significant, but small differences in favour of elacestrant compared to SOC in the overall population and the population with an *ESR1* mutation. The results seem to be mainly driven by patients with an *ESR1* mutation who have a longer PFS in the elacestrant group compared to the overall population, whereas the SOC performs similar in the *ESR1*-mut and overall group. Therefore, the indication was restricted to patients with an activating *ESR1*-mutated tumour. The differences in PFS were only observed at and after the first scan at 8 weeks, but tipping point analyses correcting for early censoring, showed that in the *ESR1*-mut population the results are robust.

The key secondary endpoint OS was not statistically different between the elacestrant and SOC arms in both the overall and *ESR1*-mut population, though reassuringly the KM curves did not show signals of a detriment.

During the study, two major changes were conducted regarding the efficacy testing procedures. The first change was an earlier than planned PFS analysis. Although the decision for changing the analysis time point seems to have been made by persons not blinded to treatment assignment, these had no access to aggregated data. In addition, additional analyses with an updated PFS analysis and stable HR ratios over time support that the final PFS analysis provided can be regarded as a reliable alternative to the originally planned final analysis. Regarding the second amendment, the OS testing procedure was changed late in the conduct of an open-label study. This change was motivated by external advice from the FDA and no data from the ongoing study was used to inform the changes made. As neither

the interim nor the final OS analysis showed a statistically significant effect on OS, there is also no impact of the late definition of the multiplicity procedure on the interpretation of the OS analysis. Based on this, it is considered that the internal validity of the study was maintained irrespective of the changes in the testing procedures and that the presented efficacy results do allow for an adequate B/R assessment. An additional issue identified is the discordance between independent and investigator review of PFS with the risk of informative censoring biasing IRC-assessed PFS in the elacestrant arm. However, a gain of median PFS of 1.58 months was reported for investigator-assessed PFS in favour of elacestrant in *ESR1*-mut patients (which was absent in the overall population).

With regards to the remaining uncertainty on the choice for the recommended posology as the B/R assessment was made on the posology used in the pivotal study, the recommended posology is considered to be based on efficacy and safety results from the pivotal study.

Overall, the safety profile of the oral SERD elacestrant in the proposed target population resembles that known for endocrine therapies and especially fulvestrant. The main difference is a marked increase in GI toxicity, especially nausea and vomiting, which may be partly related to the difference in route of administration when compared to fulvestrant. Most events are mild to moderate and discontinuations or dose reductions occurred at low rates. Other AEs known for ET like fatigue/asthenia, elevated hepatic enzymes, hot flushes and musculoskeletal and joint pain were observed at the same order of magnitude as for the SOC. Grade 3 or 4 AEs occurred in about a quarter of patients with a higher incidence compared to the SOC, whereas SAEs were reported in a similar proportion. The safety profile of the SOC is in line with that known and reflected in the SmPC, no new safety signals were identified.

3.7.2. Balance of benefits and risks

In the population with an activating *ESR1* mutation the primary endpoint IRC-assessed PFS showed a significant median increase of 1.9 months in favour of elacestrant compared to SOC. Although this is a small increase it is considered of clinical relevance and outweighs the identified risks with a clinically manageable safety profile.

The results for the overall population seem to be mainly driven by patients with an *ESR1* mutation who have a longer PFS in the elacestrant group compared to the overall population, but the SOC performs similar in the *ESR1*-mut and overall group. No benefit over SOC is obvious in *ESR1*-mut-nd population, i.e. patients with wild type *ESR1* and unknown mutation status. Consequently, the therapeutic indication has been restricted to patients with ER-positive, HER2-negative advanced breast cancer with an activating *ESR1* mutation. Patients with ER-positive, HER2-negative advanced breast cancer should be selected for treatment with elacestrant based on the presence of an activating *ESR1* mutation in plasma specimens, using a CE marked *in vitro* diagnostic (IVD) with the corresponding intended purpose.

Although it is known that efficacy of fulvestrant is different in patients who progressed on a CDK4/6i compared to patients CDK4/6i naïve (Lindeman et al., Clinical Cancer Research, 2022), the impact of prior CDK4/6i therapy on the activity of elacestrant is not known based on the provided data. The therapeutic indication is restricted to patients who have had received prior treatment with CDK4/6 inhibitors.

3.7.3. Additional considerations on the benefit-risk balance

While the proportion of men in the study programme is very low, it is still considered possible to extrapolate results to men, based on the common biological and pharmacological rationale.

3.8. Conclusions

The overall benefit/risk balance of Orserdu (elacestrant) is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Orserdu is favourable in the following indication(s):

Orserdu monotherapy is indicated for the treatment of postmenopausal women, and men, with estrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK4/6 inhibitor.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that elacestrant is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.