Single Technology Appraisal

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after endocrine treatment [ID6225]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission** from Menarini Stemline
    a. Full submission
    b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
    a. Breast Cancer Now – patient group
    b. Make 2nds Count – patient group
    c. METUPUK – patient group

4. **Expert personal perspectives** from:
    a. Professor Mark Beresford, Consultant Clinical Oncologist – clinical expert, nominated by Menarini Stemline
    b. Kirstin Spencer, Patient Advocate - patient expert, nominated by METUPUK
    c. Eleanor Pearce Willis, Policy Manager - patient expert, nominated by Breast Cancer Now
    d. Dr Mukesh Bindlish Mukesh, Consultant Clinical Oncologist – clinical expert nominated by Menarini Stemline

5. **External Assessment Report** prepared by Southampton Health Technology Assessments Centre (SHTAC)

6. **External Assessment Report – factual accuracy check**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Elacestrant for treating oestrogen receptor-positive, HER2-negative advanced breast cancer with an *ESR1-mut* after at least one endocrine treatment [ID6225]

Document B

Company evidence submission

May 2024

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Contents

Tables and Figures

Abbreviations

AE	Adverse event
AI	Aromatase inhibitor
AIC	Akaike information criterion
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BC	Breast cancer
BIC	Bayesian information criterion
BNF	British National Formulary
BSA	Body surface area
C	Cycle (of treatment)
CBE	Clinical benefit evaluable
CBR	Clinical benefit rate
CDK4/6i	Cyclin-dependent kinase 4/6 inhibitor
CGP	Comprehensive Genomic Profiling
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CR	Complete response
CSR	Clinical study report
ChT	Chemotherapy
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumour DNA
CYP3A4	Cytochrome P450 3A4
D	Day (of treatment cycle)
DCO	Data cut-off
DNA	Deoxyribonucleic acid
DOR	Duration of response
DSU	Decision Support Unit
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eMIT	Electronic market information tool
EORTC QLQ-C30	European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire
EOT	End of treatment
EQ-5D	EuroQol-5 Dimension
EQ-5D-3L	EuroQol-5 Dimension-3 Level
EQ-5D-5L	EuroQol-5 Dimension-5 Level
ER	Oestrogen receptor
ER+	Oestrogen receptor-positive
ERα	Oestrogen receptor-alpha
ESMO	European Society for Medical Oncology
ESR1	Oestrogen receptor 1
ESR1-mut	*ESR1* mutation
ESS	Effective sample size
ET	Endocrine therapy
EU	European Union
EU5	Five European Countries (France, Germany, Italy, Spain, United Kingdom)
FACT-B	Functional Assessment of Cancer Therapy - Breast
FSH	Follicle stimulating hormone
GnRH	Gonadotropin-releasing hormone
GP	General practitioner
HER2-	Human epidermal factor receptor 2-negative
HR	Hazard ratio
HR	Hormone receptor
HR+	Hormone receptor-positive
HRQoL	Health-related quality of life
ICD	International Classification of Disease
ICER	Incremental cost-effectiveness ratio
IM	Intramuscular
INMB	Incremental net monetary benefit
IPD	Individual patient-level data
IRC	Imaging review committee
IRT	Interactive Randomisation Technology
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
IVD	In vitro diagnostic
KM	Kaplan–Meier
KOL	Key opinion leader
L	Line (of therapy)
LH	Luteinizing hormone
LTFU	Lost to follow-up
LY	Life year

LYG	Life years gained
MA	Marketing authorisation
MAIC	Matching-adjusted indirect comparison
mBC	Metastatic breast cancer
MHRA	Medicines and Healthcare products Regulatory Agency
MMRM	mixed model repeated measures
MRI	Magnetic resonance imaging
mTORC1i	Mammalian target of rapamycin complex 1 inhibitor
NA	Not assessed
NC	Not calculated
NE	Not evaluable
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NMB	Net monetary benefit
OR	Overall response
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PartSA	Partitioned survival analysis
PAS	Patient access scheme
PD	Progressive disease
PFS	Progression-free survival
PI	Principal investigator
PI3K	Phosphatidylinositol 3 kinase
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PIK3CA-mut	*PIK3CA* mutation
PK	Pharmacokinetic(s)
PR	Partial response
PR	Progesterone receptor
PRO	Patient-reported outcome
PRO-CTCAE	Patient-Reported Outcome Common Terminology Criteria for Adverse Events
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSM	Parametric survival models
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q	Quartile
QALY	Quality-adjusted life year
QoL	Quality of life
QTcF	QT corrected for heart rate by Fridericia's cube root formula
RANKL	Receptor activator of nuclear factor kappa-B
RCT	Randomised controlled trial
RDI	Relative dose intensity
RE	Response evaluable
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	Ribonucleic acid
RWD	Real-world database
RWE	Real-world evidence
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SD	Standard deviation
SERD	Selective oestrogen receptor degrader
SERM	Selective oestrogen receptor modulator
SLR	Systematic literature review
SmPC	Summary of product characteristics
SOC	Standard of care
TA	Technology Appraisal
TEAE	Treatment-emergent adverse event
TRAE	Treatment-related adverse event
TTD	Time to treatment discontinuation
UK	United Kingdom
US	United States
VAS	Visual analogue scale
WOC	Withdrawal of consent
WTP	Willingness to pay
1L	First-line
2L	Second-line

Decision problem, description of the technology and clinical care pathway

Oestrogen (estrogen) receptor-positive (ER+)/human epidermal factor receptor 2-negative (HER2-) advanced/metastatic breast cancer (mBC) is an incurable, devastating disease with poor treatment outcomes (approximately 36% survival at 5 years), which diminish with each line of therapy.[1–3]

- Breast cancer (BC) is the leading cause of cancer in women in the United Kingdom (UK), the disease is most common in postmenopausal women (age ≥50 years).[4,5] The ER+/HER2- subtype, accounts for approximately 70% of BC cases.[6]
- Advanced/mBC causes significant morbidity and psychological distress, negatively impacting health-related quality of life (HRQoL) and daily living including physical activities, relationships, social life, work productivity and emotional well-being.[7,8]
- The burden of caring for patients with cancer can impact caregivers' physical and mental health and daily living such as work status and social activities, negatively impacting HRQoL.[9,10] ER+/HER2- advanced/mBC has a high economic and societal burden; the substantial impact of BC is highlighted in a recent report (published in January 2024) that estimated the annual total cost of BC to the UK economy to be £2.6 to £2.8 billion.[11]

Acquired resistance to endocrine therapy (ET) is a key issue in managing patients with ER+/HER2- advanced/mBC and acquired mutations in oestrogen receptor 1 (*ESR1*) are associated with acquired resistance to ET.

- For patients with ER+/HER2- advanced/mBC who do not require chemotherapy (which is mainly indicated when there is a risk of imminent organ failure), standard of care (SOC) treatment in the frontline advanced/metastatic setting is ET, with an aromatase inhibitor (AI) + cyclin-dependent kinase 4/6 inhibitor (CDK4/6i).[12]
- While 20% of patients with ER+/HER2- advanced/mBC progress rapidly on ET + CDK4/6i and are unlikely to benefit from further ET, many patients acquire resistance to ET + CDK4/6i over a longer time period.[13]
- Several molecular mechanisms have been identified that underlie the acquisition of ET resistance, including acquired mutations in *ESR1 (ESR1-mut)*, the gene which encodes for oestrogen receptor-alpha (ERα).[14] *ESR1-mut* are found in up to 50% of patients with ER+/HER2- advanced/mBC who progress on AI therapy,[15,16] and these patients have faster disease progression and worse survival than patients with ER+/HER2- advanced/mBC without an *ESR1-mut*.[17,18]

Patients with ER+/HER2- *ESR1*-mutated advanced/mBC whose disease has progressed following prior treatment with ET + CDK4/6i have limited treatment options.

- For patients with ER+/HER2- *ESR1*-mutated advanced/mBC whose disease has progressed following ≥12 months prior treatment with ET + CDK4/6i (the population of interest in this submission) there are two treatment options currently used if cytotoxic chemotherapy is not indicated:

- **Everolimus + exemestane** (National Institute for Health and Care Excellence [NICE] Technology Appraisal [TA]421) for patients without symptomatic visceral disease[19]
- **Alpelisib + fulvestrant** (NICE TA816)[20] can be used as a treatment option in patients with a phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA)* mutation

- Neither of these treatment regimens specifically target the *ESR1-mut* and both have limitations, such as toxicity (everolimus and alpelisib) and pain and inconvenience of treatment (in-clinic injections for fulvestrant administration).[20–26]
- There is a high unmet need for a targeted treatment for the population of patients with ER+/HER2- *ESR1*-mutated advanced/mBC who have disease progression with ≥12 months prior treatment with ET + CDK4/6i that delays disease progression, prolongs survival, is well-tolerated and can be taken orally, providing convenience for patients and caregivers.

Elacestrant is a next-generation oral, nonsteroidal, once-daily selective oestrogen receptor degrader (SERD) that has marketing authorisation in postmenopausal women, and men, with ER+/HER2-, locally advanced or mBC with an activating *ESR1-mut* who have disease progression following at least one line of ET including a CDK4/6i.

The submission is for a subpopulation of the marketing authorisation for elacestrant: postmenopausal women, and men, with ER+/HER2- *ESR1*-mutated advanced/mBC who have disease progression with ≥12 months of prior treatment with ET + CDK4/6i, as this is the population of patients where clinicians perceived the most value of elacestrant is in clinical practice in the UK.

B.1.1 Decision problem

Elacestrant monotherapy is indicated for the treatment of postmenopausal women, and men, with ER+/HER2-, locally advanced/mBC with an *ESR1* mutation who have disease progression following at least one line of ET including a CDK4/6i.[27]

This submission focuses on a subpopulation of the marketing authorisation: postmenopausal women, and men, with ER+/HER2-, locally advanced/mBC with an activating *ESR1* mutation who have disease progression following ≥12 months prior treatment with ET + CDK4/6i. Based on feedback from clinicians in the UK on progression free survival (PFS) data presented at the San Antonio Breast Cancer Symposium, this is where elacestrant will provide most value in UK clinical practice.[28–30]

In a *post hoc* subgroup analysis of the pivotal phase III study (EMERALD), patients treated with elacestrant had a greater improvement in PFS with longer exposure (≥12 months) to prior ET + CDK4/6i (8.6 months) vs. SOC (ET monotherapy, 1.9 months, see Section B.2.7.2.1).[28,30] The results of this *post hoc* subgroup analysis support the beneficial activity of elacestrant for patients with longer exposure (i.e. ≥12 months) to prior ET + CDK4/6i.

A summary of the decision problem is shown in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People who have been through menopause and men with ER+/HER2- locally advanced or mBC with an activating *ESR1-mut* after at least 1 line of ET including a CDK4/6i.	Postmenopausal women, and men, with ER+/HER2-, locally advanced/mBC with an activating *ESR1-mut* who have disease progression following ≥12 months prior treatment with ET + CDK4/6i.	This submission focuses on part of the technology's marketing authorisation. Postmenopausal women, and men, with ER+/HER2-, locally advanced/mBC with an activating *ESR1-mut* who have disease progression following ≥12 months prior treatment with ET + CDK4/6i. The population is narrower than the marketing authorisation because this is the population of patients where UK clinicians perceive the most value for elacestrant to be in UK clinical practice. In a *post hoc* subgroup analysis of the pivotal phase III study (EMERALD), patients treated with elacestrant had a greater improvement in PFS with longer exposure (≥12 months) to prior ET + CDK4/6i vs. ET monotherapy. The results of this *post hoc* subgroup analysis support the beneficial activity of elacestrant in patients with longer exposure (i.e. ≥12 months) to prior ET + CDK4/6i.
Intervention	Elacestrant	Elacestrant	Not applicable
Comparator(s)	Everolimus + exemestane ET with or without chemotherapy Chemotherapy For people whose BC is *PIK3CA*-mutated: alpelisib + fulvestrant	Everolimus + exemestane For people whose BC is *PIK3CA*-mutated: alpelisib + fulvestrant	This submission focuses on patients with ER+/HER2- advanced/mBC with an activating *ESR1-mut* who have disease progression following ≥12 months prior treatment with ET + CDK4/6i. After progression with ET + CDK4/6i, NICE recommends treatment with everolimus + exemestane (TA421), this is consistent with clinical practice in England and Wales and is considered the main comparator for elacestrant. NICE also recommends treatment with alpelisib + fulvestrant in patients with a *PIK3CA*-mutated tumour

			(TA816), this is consistent with clinical practice in England and Wales and is considered a comparator for elacestrant for the subpopulation of patients with both a *PIK3CA-mut* and an activating *ESR1-mut* (referred to throughout this submission as the 'dual mutated population'). Based on UK clinical expert opinion, ET monotherapy or ET + chemotherapy is rarely used, in clinical practice in England and Wales, in the patient population under consideration in this submission and as such, these are not considered relevant comparators for elacestrant.[29] Based on UK clinical expert opinion, chemotherapy in the UK is reserved predominantly for patients with imminent risk of organ failure, as such chemotherapy is not considered a relevant comparator for elacestrant in the patient population considered in this submission.[29]
Outcomes	OS PFS Response rate Adverse effects of treatment HRQoL	OS PFS Response rate Adverse effects of treatment HRQoL	Not applicable
Subgroups to be considered	Mutations in both *ESR1* and *PIK3CA*	Mutations in both *ESR1* and *PIK3CA*	This submission focuses on patients with ER+/HER2- advanced/mBC with an activating *ESR1-mut* who have disease progression following ≥12 months prior treatment with ET + CDK4/6i. Therefore, for the dual mutated population only those patients progressing following ≥12 months prior treatment with ET + CDK4/6i are considered.

Abbreviations: BC, breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER+, oestrogen receptor-positive; *ESR1* oestrogen receptor 1 gene; ET, endocrine therapy; HER2-, human epidermal factor receptor 2-negative; HRQoL; health-related quality of life; mBC, metastatic breast cancer; NICE, National Institute for Health and Care Excellence; OS, overall survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PFS, progression-free survival; UK, United Kingdom
Source: NICE final scope for elacestrant[31]

B.1.2 Description of the technology being appraised

A description of elacestrant is shown in Table 2. The Summary of Product Characteristics (SmPC) and the UK public assessment report are provided in Appendix C.

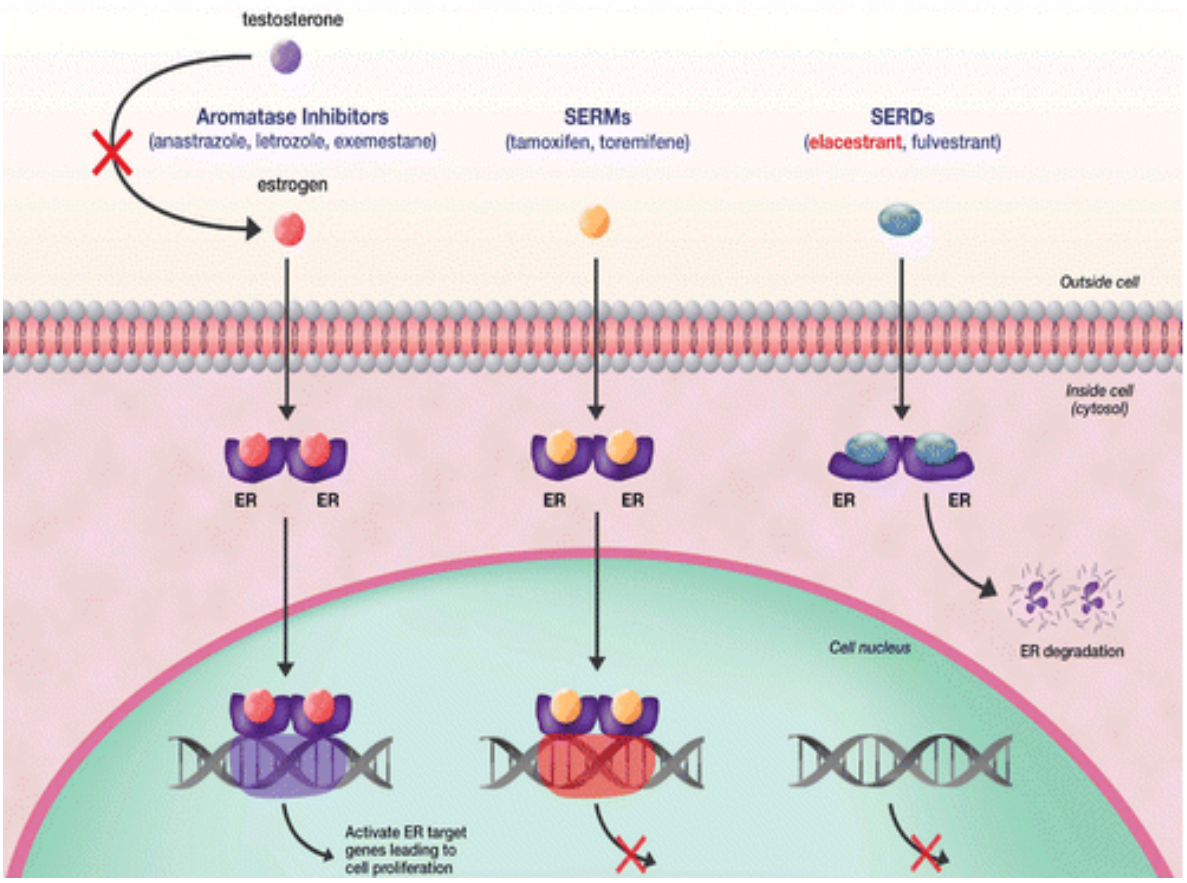
Table 2: Technology being appraised

UK approved name and brand name	Elacestrant (KORSERDU®)
Mechanism of action	Elacestrant is a next-generation, nonsteroidal, orally bioavailable SERD that binds to ERα and causes its degradation in a dose-dependent manner through the proteasomal pathway. It has been shown to inhibit oestradiol-dependent ER-directed gene transcription and tumour growth using *in vitro* and *in vivo* preclinical models, including in ER+/HER2- BC cells resistant to CDK4/6i and fulvestrant, and those with *ESR1-mut* (Figure 1).[32–34]
Marketing authorisation/CE mark status	Elacestrant was granted a UK marketing authorisation by the MHRA on 6th December 2023
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Elacestrant is indicated for the treatment of postmenopausal women, and men, with ER+/HER2-, locally advanced or mBC with an activating *ESR1-mut* who have disease progression following at least one line of ET including a CDK4/6i.[27] Contraindications[27] Hypersensitivity to the active substance or any of the excipients as follows: Tablet core: Microcrystalline cellulose [E460], silicified microcrystalline cellulose, crospovidone [E1202], magnesium stearate [E470b], colloidal silicon dioxide [E551]. Film-coating: Opadry II 85F105080 Blue containing polyvinyl alcohol [E1203], titanium dioxide [E171], macrogol [E1521], talc [E553b] and brilliant blue FCF aluminium lake [E133].
Method of administration and dosage	Elacestrant is administered as an oral tablet (345 mg) once daily as long as clinical benefit is observed or until unacceptable toxicity occurs. The tablets should be swallowed whole.[27] Patients should take their dose at approximately the same time each day, with a light meal to reduce nausea and vomiting.[27] Doses can be reduced or modified depending on adverse reactions as per the SmPC.[27]
Additional tests or investigations	Patients with ER+/HER2- advanced BC should be selected for treatment with elacestrant based on the presence of an activating *ESR1-mut* in plasma specimens, using a CE-marked IVD with the corresponding intended purpose. If a CE-marked IVD is not available, the presence of an activating *ESR1-mut* in plasma specimens should be assessed by an alternative validated test.[27] Genomic testing for *ESR1-mut* is not currently funded as standard practice. Elacestrant is the first treatment option specifically indicated for patients with ER+/HER2- *ESR1*-mutated advanced/mBC. It is anticipated that testing will be funded in the future with the introduction of elacestrant treatment. The company will factor in the cost of *ESR1* testing on liquid biopsy using feedback from an NHS laboratory, based on a test performed by PCR.

List price and the average cost of a course of treatment	Elacestrant proposed list price (excluding VAT): Cost per 28-pack of 86 mg tablets: [redacted] Cost per 28-pack of 345 mg tablets: [redacted] Elacestrant does not have a specified course duration
Patient access scheme (if applicable)	A confidential simple fixed price discount PAS has been submitted to NHS England for elacestrant Cost per 28-pack of 86 mg tablets: [redacted] Cost per 28-pack of 345 mg tablets: [redacted]

Abbreviations: BC, breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER, oestrogen receptor; DNA, deoxyribonucleic acid; ER+, oestrogen receptor-positive; ERα, oestrogen receptor-alpha; *ESR1*; oestrogen receptor 1 gene; ET, endocrine therapy; HER2-, human epidermal factor receptor 2-negative; iCT, interactive costing tool; IVD, in vitro diagnostic; mBC, metastatic breast cancer; MHRA, Medicines and Healthcare products Regulatory Agency; NHS, National Health Service; NIHR; National Institute for Health and Care Research; PAS, patient access scheme; PCR, polymerase chain reaction; SERD, selective oestrogen receptor degrader; SmPC, Summary of product characteristics; UK, United Kingdom

Figure 1: Elacestrant mechanism of action



Abbreviations: ER, oestrogen receptor; SERD, selective oestrogen receptor degrader; SERM, selective oestrogen receptor modulator
Source: Bardia *et al*. (2019)[32]

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

B.1.3.1.1 Disease description

BC is the leading cause of cancer in women and the fourth leading cause of cancer deaths, in the UK.[4] The disease occurs when abnormal cells in the ducts or lobules of the breast grow and divide uncontrollably, forming a tumour.[35] The prevalence of BC advances with age and typically occurs in women, who represent >99% of cases, the disease is most common (80% of cases) in postmenopausal women (age ≥50 years).[5,36,37]

B.1.3.1.2 Disease staging and classification

Most patients (70%) are diagnosed with early BC (Stage I to II) which is localised in the breast tissue.[11] For these patients and patients with locally advanced resectable (operable) BC (Stage III), where the cancer has spread beyond the breast to lymph nodes close to the breast or skin of the chest or chest wall, surgery is potentially curative.[38,39]

Advanced/mBC[a] encompasses patients with unresectable (inoperable) Stage III locally advanced BC and Stage IV mBC (when cancer has spread [metastasised] outside of the breast to other parts of the body such as the bones, brain, liver and lungs).[40,41] Approximately 35% of people with early or locally advanced resectable BC will progress to mBC within 10 years of diagnosis and approximately 13% of people with BC will have advanced/mBC at diagnosis.[42,43] Advanced/mBC is incurable and treatment aims to delay progression and extend survival while maintaining good quality of life.

BC tumours are classified into histopathological subtypes depending on the presence (+) or absence (-) of hormone receptors (HR) for oestrogen (ER) and/or progesterone (PR), and HER2 which promote tumour growth. The most common subtype of BC is ER+/HER2-, accounting for approximately 70% of BC cases.[6] ER+/HER2- advanced/mBC is an incurable, devastating disease with poor treatment outcomes (approximately 36% survival at 5 years), which diminish with each line of therapy.[1–3]

B.1.3.1.3 Emergence of *ESR1-mut* during endocrine therapy

For patients with ER+/HER2- advanced/mBC who do not require chemotherapy (which is mainly indicated when there is a risk of imminent organ failure),[12] initial SOC treatment in the advanced/metastatic setting is ET i.e. AI + CDK4/6i (see B.1.3.4.2 for further details on the UK treatment pathway). The establishment of ET + CDK4/6i as SOC treatment has led to longer ET exposure in the advanced/metastatic setting.[44–46]

Despite advances in treatment with the addition of CDK4/6i to ET, patients ultimately experience disease progression.[13] Approximately 20% of advanced/mBC patients progress rapidly on ET + CDK4/6i and are unlikely to benefit from further ET. The remaining patients, who exhibit ER-driven disease, acquire resistance to ET + CDK4/6i treatment over time.[13]

[a] Throughout this submission advanced/mBC is used to collectively refer to patients with unresectable locally advanced or mBC, references cited may be specific to locally advanced or mBC or both.

Several molecular mechanisms have been identified that underlie the acquisition of ET resistance, including acquired mutations in *ESR1*, the gene which encodes for ERα.[14] *ESR1-mut* are clustered in the ligand-binding domain of ERα, resulting in a ligand-independent, constitutively active conformation.[14,47] The acquisition of *ESR1-mut* in patients with ER+/HER2- advanced/mBC occurs almost exclusively after treatment with an AI and occurs more frequently with longer exposure to ET, with a higher prevalence of *ESR1-mut* in those treated with AI + CDK4/6i vs. AI alone.[13,47–49] Up to 50% of patients who have received AI treatment have *ESR1-mut* on disease progression.[15,16] Thus, a novel population of patients with ER+/HER2- *ESR1*-mutated advanced/mBC has emerged. This patient population has faster disease progression and worse survival than patients with ER+/HER2- advanced/mBC without an *ESR1-mut* (Section B.1.3.1.4).[17,18]

Mutations in *ESR1* result in oestrogen-independent ER activation, and consequently, cancer growth, metastasis, and loss of sensitivity to further treatment with AIs, but not other ETs such as SERDs, which have a different mechanism of action to AIs.[33,50] Elacestrant is a next-generation oral SERD that degrades the ERα in a dose-dependent manner and inhibits oestrogen-dependent tumour growth, including tumours with *ESR1* mutations and resistant to CDK4/6i and fulvestrant.[32–34] Therefore, patients with ER+/HER2- *ESR1*-mutated advanced/mBC who have disease progression following ≥12 months prior therapy with ET + CDK4/6i are unlikely to benefit from further AI treatment but do have the potential to get value from treatment with elacestrant, which can help overcome *ESR1*-mediated, acquired resistance to ET.

Understanding how to overcome *ESR1*-mediated acquired resistance to ET with targeted therapy is an important consideration when treating patients with ER+/HER2- *ESR1*-mutated advanced/mBC.[32,51]

B.1.3.1.4 *ESR1-mut* are a poor prognostic factor in patients with ER+/HER2- advanced/mBC

ESR1-mut have a substantial, negative impact and are a negative prognostic biomarker for PFS and overall survival (OS) outcomes.

In a secondary analysis of the BOLERO-2 trial that compared exemestane + everolimus vs. exemestane alone in patients with HR+/HER2- mBC who had progressed on an AI and were randomised to exemestane + everolimus vs. exemestane alone, Chandarlapaty *et al*. reported that of 541 evaluable patients, 156 (28.8%) had *ESR1-mut* D538G (21.1%) and/or *ESR1-mut* Y537S (13.3%), and 30 patients (5.5%) had both.[52] These mutations were associated with shorter OS (wild-type, median of 32 months; D538G, median of 26 months; Y537S, median of 20 months; both mutations, median of 15 months), indicating that *ESR1-mut* are an adverse prognostic biomarker associated with more aggressive disease biology. Additionally, median PFS was found to be shorter in patients with *ESR1*-mutated tumours vs. patients without *ESR1*-mutated tumours (5.8 months in *ESR1*-mutated tumours [D538G], 4.2 months in *ESR1*-mutated tumours [Y537S] and 5.4 months in *ESR1*-mutated tumours [D538G+Y537S] vs. 8.5 months in patients without *ESR1*-mutated tumours).[52]

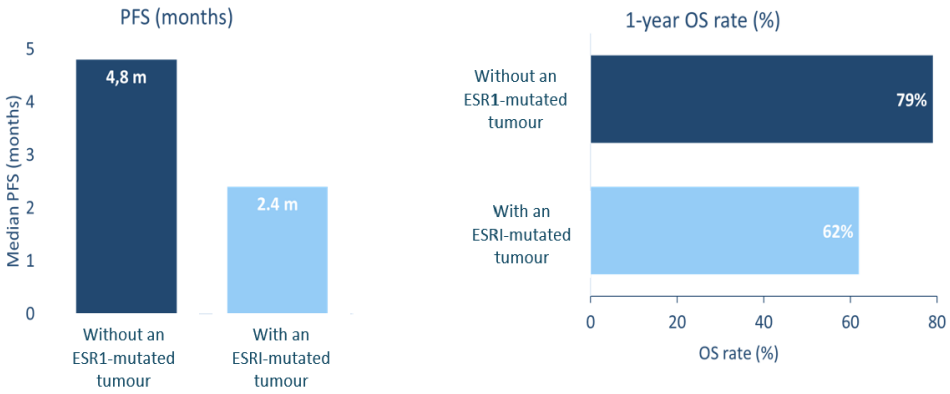
Similarly, Clatot *et al*. reported a retrospective analysis of predictive and prognostic values of circulating *ESR1-mut* (D538G and Y537S/N/C) in patients with HR+ mBC after progression on AI treatment. Among the 141 patients analysed, the median OS was significantly shorter in patients with a circulating *ESR1-mut* (15.5 months) than in patients without mutations

(23.8 months; p=0.0006; hazard ratio [HR]=1.9). PFS was also reduced in patients with *ESR1-mut*, with a median of 5.9 months vs. 7.0 months for patients without mutations (p=0.002, HR=1.7).[53]

Based on a combined analysis of the phase III EFECT and SoFEA trials of patients with ER+/HER2- after prior ET, patients with *ESR1*-mutated tumours had poorer OS than patients without *ESR1*-mutated tumours (Figure 2).[18] Patients with *ESR1*-mutated tumours also had an increased risk of progression vs. patients without an *ESR1*-mutated tumour. (Figure 2).[18]

While the EFECT and SoFEA trials did not include patients with prior exposure to CDK4/6i, they did demonstrate a consistent result in terms of inferior outcomes for patients with *ESR1*-mutated tumours vs. patients with non-detectable *ESR1-mut*.

Figure 2: Effect of *ESR1-mut* status on PFS and OS in patients with ER+/HER2- mBC in a combined analysis of the EFECT and SoFEA studies



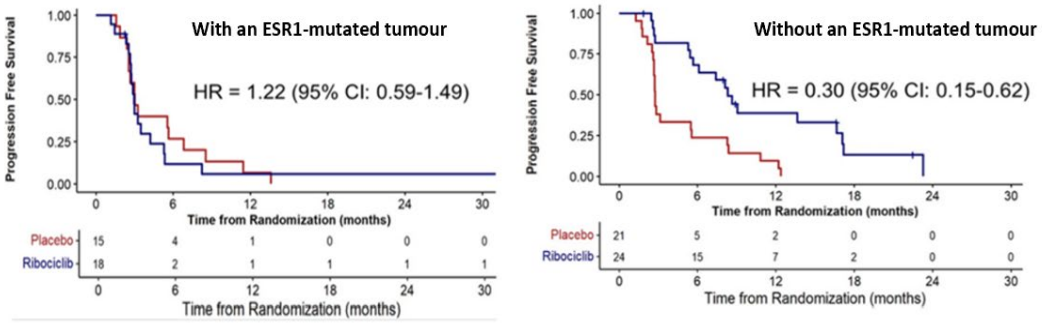
Abbreviations: ER+, oestrogen receptor-positive; *ESR1*, oestrogen receptor 1 gene; HER2-, human epidermal growth factor receptor 2-negative; m, months; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival
Source: Turner *et al*. (2020)[18]

An exploratory analysis of the phase II BYLieve study of alpelisib + ET in patients with advanced ER+/HER2- mBC and *PIK3CA-mut* previously treated with CDK4/6i assessed PFS by baseline *ESR1-mut* status.[54] In patients with prior fulvestrant + CDK4/6i treated with alpelisib + letrozole, baseline *ESR1-mut* was significantly associated with shorter PFS vs. patients without *ESR1-mut* (4.6 months vs. 7 months; HR=0.55; 95% confidence interval [CI]: 0.32, 0.92). Similar numerical trends were observed with other treatment combinations.[54]

PFS was also shorter for patients with ET-refractory ER+/HER2- advanced BC previously treated with CDK4/6i. In the biomarker subgroup analysis of the TRINITI-1 single-arm phase I/II study investigating ribociclib in combination with exemestane + everolimus, patients with *ESR1*-mutated tumours had numerically shorter median PFS than those without an *ESR1*-mutated tumour (2.8 months vs. 9.1 months).[55]

In the phase II MAINTAIN trial of ribociclib + fulvestrant in patients with prior ET + CDK4/6i exposure (n=120), median PFS was shorter in patients with *ESR1*-mutated tumours vs. patients without an *ESR1*-mutated tumour (2.96 months and 8.32 months, respectively; Figure 3).

Figure 3: PFS by baseline *ESR1-mut* in patients with HR+/HER2- mBC in the MAINTAIN trial



Abbreviations: CI, confidence interval; *ESR1*, oestrogen receptor 1 gene; HER2-, human epidermal growth factor receptor 2-negative; HR, hazard ratio; HR+, hormone receptor-positive; mBC, metastatic breast cancer; PFS progression-free survival
Source: Kalinsky *et al*. (2023)[17]

B.1.3.2 Epidemiology

B.1.3.2.1 Incidence and prevalence

An estimated 600,000 people in the UK have a diagnosis of BC, and prevalence is expected to rise to 1.2 million by 2030.[37] UK incidence rates are expected to increase to around 69,900 new cases of BC every year by 2038–2040.[56]

There is a lack of published prevalence and incidence data for patients with ER+/HER2- *ESR1*-mutated advanced/mBC in England and Wales. Based on published sources and clinical expert opinion, an estimated 2,559 patients are anticipated to be eligible to receive elacestrant in year 1 (see Budget Impact assessment for further details).

B.1.3.3 Burden of advanced or metastatic breast cancer

B.1.3.3.1 Clinical burden

BC is associated with breast and non-breast symptoms; the first noticeable symptom is usually a lump in the breast.[57,58] Other symptoms include changes in breast appearance (puckering, dimpling, rash), nipple discharge, breast infection and breast pain.[57,58] BC is also associated with numerous debilitating physical symptoms including chronic pain, nausea, fatigue, constipation, trouble sleeping and weight loss.[57,58]

Symptom burden is highest for patients whose disease has metastasised.[59, 60] Additional symptoms related to metastases vary depending on the site; for example, patients with liver metastases may experience pain on the right side of the abdomen, jaundice and nausea,

while those with brain metastases may experience seizures, difficulty speaking and loss of vision.[59] In a study of patients with HER2- Stage IV mBC (n=102) in the United States (US), disease progression was associated with clinically relevant worsening of symptoms.[60] The symptoms sensitive to the general effects of disease progression or site of metastasis were physical pain, fatigue and trouble sleeping.[60]

Pain, fatigue, and insomnia are the symptoms that patients report as being most severe: in a real-world study of women with HR+/HER2- advanced BC (n=252) across five European countries (EU5), of patients experiencing pain, 80% rated their pain as moderate/severe.[61]

A cross-sectional study of patients with HR+/HER2- advanced BC (n=15) reported fatigue/tiredness/poor energy level as the most bothersome symptom for all patients (100%) followed by pain, including bone pain (87%), difficulty concentrating (87%), hot flushes (87%) and memory loss (80%).[62]

Treatment side effects are an additional burden to patients. In a study of patients with HR+/HER2- advanced/mBC across seven countries (n=467), 82% of patients experienced ≥1 moderate- or severe-grade side effect since the commencement of their current treatment with 67% and 20% of patients experiencing ≥3 and ≥5 side effects, respectively.[63]

B.1.3.3.2 Patient burden

The symptoms of advanced/mBC cause significant morbidity and psychological distress, substantially negatively impacting HRQoL and daily living, and impairing physical activities, relationships, social life, work productivity and emotional well-being.[7,8]

More than half of women with mBC (58%), report their family well-being is 'very much' impacted and a fifth (20%) report the disease has greatly affected their responsibilities and social life.[64]

Approximately 36% of women state that they no longer work and were forced to retire due to their disease (median age at diagnosis of ER+/HER2- mBC is approximately 66 years).[64,65] The impact of BC on work is further highlighted by a US longitudinal study, which reported BC progression was correlated with a low probability of employment and increased hours missed in the workplace.[66]

In a cross-sectional study of patients with HR+/HER2- advanced/mBC (n=15), patients reported that their disease impacted leisure activities (67%), the ability to maintain relationships (47%), moving from full-time to part-time work (27%) and sleeping due to pain and discomfort (27%).[7] The most frequently reported impacts of their disease on physical functioning were housework (73%), walking (73%) and cooking (73%):[7]

> "*I don't want to do [anything]. Eat, cook, clean, nothing. I'm just that tired and I'll go right to sleep."* [7]
>
> "*You don't want to walk long distances unless you're with someone. Even if you're with someone you don't want to walk long distances because you become tired quicker."* [7]
>
> *"I know that I'm a very good cook but now, in the kitchen, that's tiresome."* [7]

In addition to the direct impact of symptoms on daily living, patients suffer from significant psychological problems such as depression and anxiety.[67,68] Distress, feelings of isolation,

reduced self-worth, and changes in body image and sexuality also negatively impact emotional well-being.[69]

Chemotherapy treatment is burdensome and can cause severe toxicity and deterioration in HRQoL including hair loss, weight loss, nausea and fatigue and a decline in physical, mental and emotional well-being.[70,71] Treatment with chemotherapy may also require in-clinic intravenous (IV) administration and hospital stays.

B.1.3.3.3 Carer burden

Patients with ER+/HER2- advanced/mBC often require daily assistance from informal carers, such as family and friends. Aside from the patient burden, the burden of caring for patients with cancer can impact caregivers' physical and mental health and daily living such as work status and social activities, negatively impacting HRQoL.[9,10]

Carers may experience an increased burden when the patient receives chemotherapy, including travelling to medical appointments and increased care due to treatment toxicity. Specifically, carers report low self-efficacy in care provision and insecurity in managing chemotherapy adverse events (AEs).[72]

New targeted treatment options for patients with ER+/HER2- *ESR1*-mutated advanced/mBC after disease progression following ≥12 months prior treatment with ET + CDK4/6i will delay time to cytotoxic chemotherapy, reducing both the patient and carer burden.

B.1.3.3.4 Health-related quality of life burden

Patients with ER+/HER2- advanced/mBC experience diminished HRQoL, which deteriorates further as the disease worsens.[61,73] Thus, treatments should aim to maintain or improve HRQoL.

Many studies have reported on the HRQoL of patients with advanced/mBC. In a cross-sectional study of patients with mBC (n=96) in Germany, lower HRQoL scores were reported in patients with mBC than those of the representative normative population across all HRQoL measures, with the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) capturing most aspects of HRQoL.[74] The difference in the EORTC QLQ-C30 functional scale, symptom scale and overall state of health scores were significantly worse for patients with mBC vs. the normative population ($p<0.0001$).[74]

In a cross-sectional survey of patients with mBC in the UK (n=235) who completed the Functional Assessment of Cancer Therapy - Breast (FACT-B) a self-administered questionnaire, scores for physical, social/family, emotional, functional and functional well-being were lower (reflecting lower HRQoL) for patients with mBC vs. normative data derived from the 295-patient validation sample for the FACT-B questionnaire, where only 20% of women had distant metastases.[8,75]

Disease progression decreases HRQoL with each additional line of therapy. In a study by Lloyd *et al*. examining HRQoL in patients with mBC in the UK (n=100), disease progression had the largest impact on HRQoL (utility value -0.272).[76] A multicentre, health utility study conducted in five EU countries (n=613) and the US (n=126) in patients with ER+/HER2- advanced/mBC reported significantly lower mean EuroQol-5 Dimension (EQ-5D) index scores for patients on second-line (2L) therapy vs. patients on first-line (1L) therapy

(p=0.0001), highlighting the need for treatment options that maintain/improve patient HRQoL.[73]

Treatment-related side effects reduce HRQoL. In a study of patients with HR+/HER2- advanced BC across seven countries (n=467), the majority of patients (78%) believed that treatment side effects affecting daily living had a moderate or severe impact on their HRQoL.[63] In the study by Lloyd *et al*. toxicities due to chemotherapy led to a decline in utility of at least 0.103, underlining the importance of delaying the use of cytotoxic chemotherapy.[76]

Given that patients with ER+/HER2- *ESR1*-mutated advanced/mBC have faster disease progression and worse prognosis than patients without an *ESR1-mut*,[17,18] and HRQoL declines each time a patient progresses,[73,76] it can be assumed that patients with *ESR1*-mutated tumours experience a more rapid decrease in HRQoL across treatment lines than patients without *ESR1*-mutated tumours.

These data highlight the need for future treatment options that reduce disease progression (maintaining or improving HRQoL) and that are well-tolerated, minimising treatment side effects and avoiding a further reduction in HRQoL.

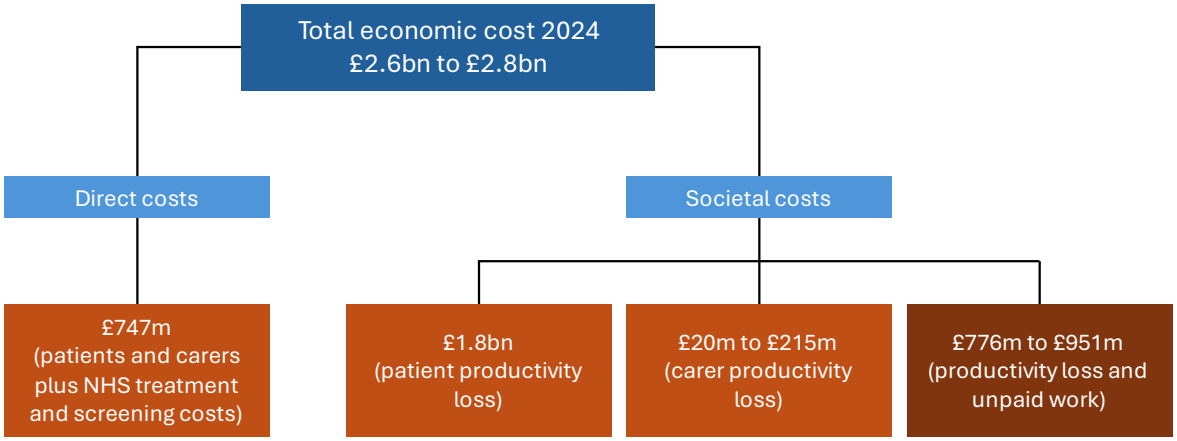
B.1.3.3.5 Economic and societal burden of advanced or metastatic breast cancer

ER+/HER2- advanced/mBC has a high economic and societal burden. The yearly cost of BC to the UK economy is estimated at £2.6 to £2.8 billion in 2024 (Figure 4), which is approximately 0.1% of the UK gross output.[11] By 2034, the total yearly cost of BC to the economy would rise to £3.6 billion in the absence of disease prevention.[11] Although the direct costs of BC to the NHS are substantial, societal costs make up the majority of costs (Figure 4).[11]

Societal costs of advanced/mBC are not included in the economic evaluation in this submission. However, it is important to consider the positive benefits that new treatment options could provide i.e. improved PFS is likely to lead to increased work productivity and reduced absenteeism for both patients and carers.

In 2024, the total well-being cost associated with BC (including patients' reduced HRQoL/early mortality, carer/partner well-being loss, and anxiety in children) is estimated at £17.5 billion.[11] This is not cash spent, but is representative of the human costs of BC, providing a useful estimate for policy options which may reduce some of the loss of well-being.[11]

Figure 4: Total economic costs (direct and societal) of BC in the UK in 2024



Abbreviations: BC, breast cancer; bn, billion; m, million
Source: Breast Cancer Now (2024)[11]

B.1.3.4 Current treatment pathway and proposed elacestrant positioning

B.1.3.4.1 Current guidelines/guidance

Currently, there are no specific guidelines/guidance for the population of patients with ER+/HER2- *ESR1*-mutated advanced/mBC in England and Wales.

The guidelines/guidance most consistent with clinical practice in England and Wales are NICE TAs for ER+/HER2- advanced/mBC, the European Society for Medical Oncology (ESMO) Guideline for mBC and the ESMO mBC Living Guideline for patients with ER+/HER2- mBC.[29]

A summary of relevant TAs is provided in Table 3. The ESMO mBC Living Guideline (published in 2023) incorporates the recommendations from the ESMO Guideline (published in 2021) and a summary is provided in Table 4.[12,77]

Other NICE guidelines include NICE CG81 (advanced BC), last updated on 16 August 2017 and NICE Guideline (NG)101, (early and locally advanced BC), last updated on 16 January 2024.[78,79] A summary of these guidelines is provided in Appendix M.[b]

[b] The NICE 2023 surveillance of early and locally advanced breast cancer: diagnosis and management (NICE guideline NG101) and advanced breast cancer: diagnosis and treatment (NICE guideline CG81) report also provides recommendations for updates to CG81 and NG101.[80]

Table 3: Summary of the most relevant published NICE TAs for ER+/HER2- advanced/mBC

Appraisal ID	Year	Intervention	Title
TA421[19]	2016	Everolimus + exemestane	Everolimus with exemestane for treating advanced breast cancer after endocrine therapy
TA816[20]	2022	Alpelisib + fulvestrant	Alpelisib with fulvestrant for treating hormone receptor-positive, HER2-negative, *PIK3CA*-mutated advanced breast cancer
TA495[81]	2017	Palbociclib + AI	Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer
TA496[82]	2017	Ribociclib + AI	Ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer
TA563[83]	2019	Abemaciclib + AI	Abemaciclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer
TA836[84]	2022	Palbociclib + fulvestrant	Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy
TA725[85]	2021	Abemaciclib + fulvestrant	Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy
TA687[86]	2021	Ribociclib + fulvestrant	Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy
TA423[87]	2016	Eribulin	Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens
TA116[88]	2007	Gemcitabine	Gemcitabine for the treatment of metastatic breast cancer

Abbreviations: AI, aromatase inhibitors; HER2, human epidermal growth factor receptor 2; NICE, National Institute for Health and Clinical excellence; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TA, technology appraisal
Source: NICE website

Table 4: Summary of the ESMO mBC Living Guideline for patients with ER+/HER2- mBC

Line of therapy	Summary
1L	• CDK4/6 inhibitor combined with ET • Chemotherapy if imminent organ failure
2L	• Optimal sequence of ET is uncertain after progression on CDK4/6i, and is dependent on which agents were used previously, duration of response to previous ET, mutational status, disease burden, patient preference and treatment availability • Alpelisib + fulvestrant for patients with *PIK3CA*-mutated tumours, with prior exposure to an AI (±CDK4/6i) • Elacestrant for patients with an *ESR1*-mutated tumour • Everolimus + exemestane • Everolimus + fulvestrant (preferred over everolimus + exemestane if the patient is *ESR1-mut* positive) • Switch ET ± CDK4/6i or fulvestrant monotherapy • Chemotherapy for patients at imminent risk of organ failure

Abbreviations: 1L, first-line; 2L, second-line; AI, aromatase inhibitors; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER, oestrogen receptor; ESMO, European Society for Medical Oncology; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PS, performance status; SOC, standard of care
Source: Gennari *et al*. (2021)[77]; Curigliano *et al*. (2023)[12]

B.1.3.4.2 Current treatment pathway based on NICE guidelines/guidance

Treatment for advanced/mBC aims to improve or maintain HRQoL by reducing symptoms, slowing disease progression, extending life, and minimising treatment side effects.

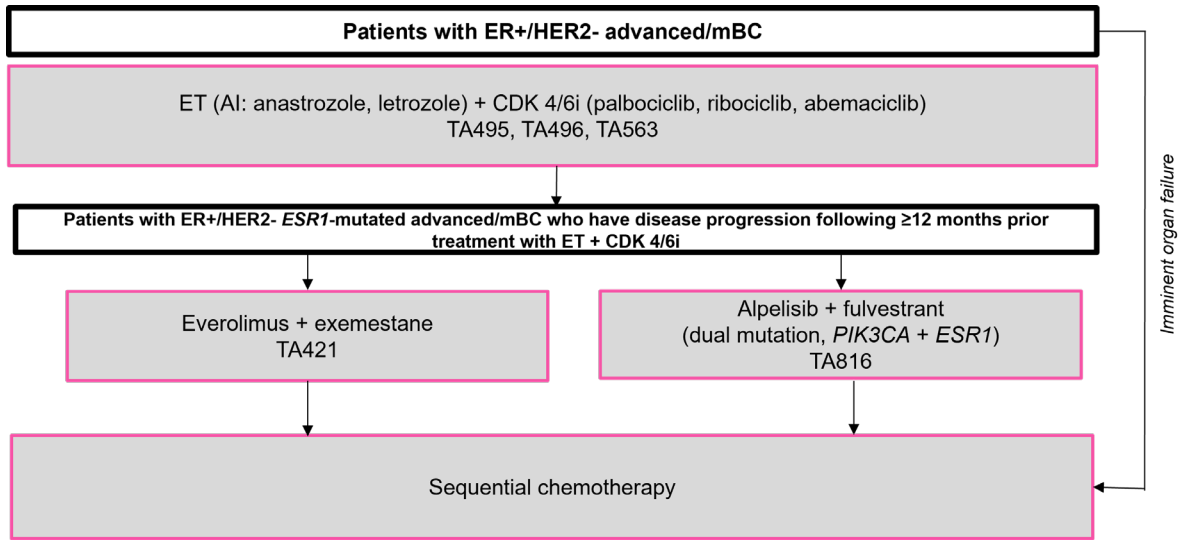
The current treatment pathway for patients with ER+/HER2- advanced/mBC and patients with ER+/HER2- *ESR1*-mutated advanced/mBC who have disease progression following ≥12 months' prior treatment with ET + CDK4/6i in England and Wales is summarised in Figure 5. In the absence of specifically targeted treatment options for patient with *ESR1*-mut, *ESR1-mut* is not proactively identified at the time of treatment progression, despite compelling evidence indicating the detrimental effects that *ESR1-mut* has on patient and treatment outcomes. Patients with *ESR1-mut* are currently managed empirically, with non-targeted medicines.

NICE TA495, TA496 and TA563 recommend treatment with ET (i.e. an AI; anastrozole and letrozole) + CDK4/6i (palbociclib, ribociclib or abemaciclib) for patients with ER+/HER2- advanced/mBC.[81–83] Treatment with chemotherapy is mainly reserved for patients with imminent organ failure.[12,77]

For patients with ER+/HER2- *ESR1*-mutated advanced/mBC who have disease progression following ≥12 months prior treatment with ET + CDK4/6i, there are currently two treatments that are considered in clinical practice: 1) everolimus + exemestane (NICE TA421) for patients without symptomatic visceral disease [19] and; 2) alpelisib + fulvestrant (NICE TA816).[20] Alpelisib + fulvestrant can be used as a treatment option in patients with a single

PIK3CA-mut, including those patients with both a *PIK3CA-mut* and an *ESR1-mut* (dual mutated).

Figure 5: Current treatment pathway in England and Wales



Abbreviations: AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER+, oestrogen receptor-positive; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; HER2-, human epidermal growth factor receptor 2-negative; mBC, metastatic breast cancer; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TA, technology appraisal

B.1.3.4.2.1 Genomic testing in advanced/mBC

To aid clinicians in making targeted treatment decisions, genomic testing has become an integral component of treatment planning and is increasingly used at various points in the treatment pathway for patients with advanced/mBC.[89] *ESR1-mut* arise almost exclusively after previous exposure to an AI in the advanced/metastatic setting, as a result of the selective pressure of endocrine deprivation therapies, and are typically undetectable in the primary tumour.[47] Thus, in order to be eligible for elacestrant, testing should be performed at the point of clinically suspected and/or radiologically confirmed progression after at least one line of ET and a CDK4/6i. In the EMERALD trial, *ESR1* mutational status was determined by blood circulating tumour DNA (ctDNA) based assays.[33]

In the context of clinical practice in the UK, performing tissue biopsies upon progression following initial treatment for advanced/mBC is infrequent.[29] In addition, intertumoral and/or intratumoral heterogeneity and temporal evolution under exposure to specific treatments in mBC is common,[90] and tissue biopsy is generally not a suitable approach to capture the mutational burden across all metastatic sites.[91] There is an independent distribution of *ESR1* mutations between plasma and tumour tissue, and tissue-based assays may identify lower proportions of *ESR1-mut* than ctDNA based assays. This underscores the importance of utilising liquid biopsies on ctDNA to perform *ESR1-mut* testing. This approach allows for obtaining results via a minimally invasive test, within a timeframe that is relevant to clinical decisions, facilitating the optimal planning and implementation of informed treatment strategies for the patient.

The NHS does not currently fund genomic testing for *ESR1-mut* since elacestrant is the first available therapy for patients with ER+/HER2- *ESR1*-mut advanced/mBC. Future funding is expected, in line with genomic testing for *PIK3CA-mut*. At the time of the appraisal of alpelisib + fulvestrant for treating ER+/HER2-, *PIK3CA-mut* advanced/mBC (TA816), *PIK3CA-mut* testing was not routinely funded.[20] The genomic test for *PIK3CA-mut* is now included in the latest National Genomic Test Directory for Cancer (solid tumours; code M3.6).[92]

B.1.3.4.2.2 Limitations of treatments after prior ET + CDK4/6i

Limitations of the two currently available treatment regimens (everolimus + exemestane or alpelisib + fulvestrant) for patients with ER+/HER2- *ESR1*-mutated advanced/mBC who have disease progression following ≥12 months prior treatment with ET + CDK4/6i are described in Table 5. There is a high unmet need for targeted treatment options for this population of patients.

Table 5: Limitations of current treatments 2L+ setting

Treatment	Limitations
Everolimus + exemestane	Data limitations: • Lack of available phase III trial in patients who have progressed on ET + CDK4/6i therapy (efficacy only in patients who have relapsed or progressed on AI monotherapy [BOLERO-2 phase III])[22,47] • Lack of prospective data in patients with *ESR1-mut* positive tumours[47] Treatment limitations: • Frequent Grade 3/4 AEs include but are not limited to stomatitis, pneumonitis, hyperglycaemia, infections, diarrhoea, neutropenia, and thrombocytopenia[24] – Stomatitis is the most common AE and occurs very quickly with everolimus treatment (within 8 weeks of starting treatment)[24] – The most common adverse reactions leading to discontinuation are pneumonitis (including interstitial lung disease), stomatitis, fatigue, and dyspnoea[23] • In TA816 the clinical experts noted that AEs associated with everolimus limit its use[20] • AEs increase the treatment burden[20] • *ESR1-mut* predicts poor response to single-agent AI e.g. exemestane and therefore blunts the response to AI + mTORC1i due to resistance to the ET backbone[47]
Alpelisib + fulvestrant	Data limitations: • No robust phase III data; only 20 patients (5.9%) enrolled in SOLAR-1 had received prior treatment with a CDK4/6i, so no robust conclusions can be drawn regardless of how long they received a CDK4/6i for in the trial[25] • No analysis of BYLieve data in patients with *ESR1-mut* who had received ≥12 months prior treatment with CDK4/6i. No OS reported[23] • Lack of prospective data in patients with *ESR1-mut* positive tumours[47] Treatment limitations: – The most frequent Grade 3/4 events include, but are not limited to hyperglycaemia (39.1%), rash (19.4%), gamma-glutamyl transferase increased (12.0%), lymphocyte count decreased (9.2%), diarrhoea (7.0%), lipase increased (7.0%), hypokalaemia (6.3%), fatigue (5.6%), weight

	decreased (5.3%), anaemia (4.9%), hypertension (4.6%), alanine aminotransferase increase (4.2%), nausea (2.8%), creatinine increase (2.8%) and stomatitis (2.5%)[93] – As hyperglycaemia may occur with rapid onset, additional monitoring is required in the first 4 weeks of treatment with alpelisib[93] – Clinical experts in TA816 highlighted the toxicity profile of alpelisib could be difficult for some people to tolerate[20] • AEs increase the treatment burden • Fulvestrant is associated with poor bioavailability, requiring a 500 mg loading dose followed by two 250 mg/5 ml IM injections each month[26,47] • Fulvestrant IM injection requires in-clinic administration (increasing healthcare utilisation and causing inconvenience to patients and carers)[26] • Fulvestrant (21-gauge, 1.5-inch needle) administration causes injection site reactions (pain and inflammation), joint and musculoskeletal pain and allergic reactions[26]

Abbreviations: AE, adverse event; AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; IM, intramuscular; mTORC1i, mammalian target of rapamycin complex 1 inhibitor; RCTs, randomised controlled trials; TA, technology appraisal
Source: Baselga *et al*. (2011)[22]; NICE TA816[20]; Rugo *et. al* (2014)[23]; Everolimus Full Prescribing Information[24]; André *et al*. (2019)[25]; Fulvestrant Full Prescribing Information SmPC[26]; Alpelisib Full Prescribing Information[21]; Alpelisib SmPC[93]; Brett *et al*. (2021)[47]

B.1.3.5 Unmet need

There are currently no treatment options indicated or recommended in England and Wales specifically tailored to patients with *ESR1-mut* (unlike alpelisib, which targets the *PIK3CA* mutation). With the introduction of ET+ CDK4/6i, and the associated rise in the prevalence of *ESR1* mutations associated with prolonged duration of treatment, there is an increasing unmet need for a treatment specifically tailored for patients with *ESR1*-mut. Currently recommended treatments, everolimus + exemestane or alpelisib + fulvestrant, have no published data for patients with ER+/HER2- *ESR1*-mutated advanced/mBC who have disease progression following ≥12 months of prior treatment with ET + CDK4/6i. Understanding how to overcome *ESR1*-mediated acquired resistance to ET with targeted therapy is an important consideration when treating patients with ER+/HER2- *ESR1*-mutated advanced/mBC.[32,51]

In addition to the limitations in the data, current treatment options for patients with ER+/HER2- *ESR1*-mutated advanced/mBC who have disease progression following ≥12 months of prior treatment with ET + CDK4/6i have limitations, such as significant toxicity (everolimus and alpelisib) and pain and inconvenience of treatment (in-clinic injections for fulvestrant administration).[21–26]

Patients with advanced/mBC prefer oral treatments that allow them to continue their normal lives without the pain and inconvenience of injections.[94] Oral, tailored treatment for patients with *ESR1*-mutated tumours may reduce healthcare utilisation and provide convenience for both patients and carers (by avoiding frequent visits to clinics for treatment administration).

Despite advances in available therapies for patients with ER+/HER2- advanced/mBC, there remains a high unmet need for a tailored treatment for the population of patients who have ER+/HER2- *ESR1*-mutated advanced/mBC who have disease progression following ≥12 months of prior treatment with ET + CDK4/6i, that delays disease progression, is well-tolerated and can be taken orally, providing convenience for patients and caregivers.

The wider societal benefits such as increased work productivity and reduced absenteeism (for patients and carers), should also be considered when appraising novel treatment options as they are not included in the economic evaluation.

B.1.3.6 Proposed place of elacestrant in therapy

Elacestrant is a next-generation oral, nonsteroidal, once-daily SERD that acts by binding and targeting the ER for degradation. In the presence of oestrogen, it inhibits oestrogen-dependent tumour growth and has been shown to inhibit growth in tumours with *ESR1-mut* with fulvestrant and CDK4/6i-resistant tumours.[95–97]

Elacestrant is indicated for the treatment of postmenopausal women, and men, with ER+/HER2- locally advanced or mBC with an activating *ESR1-mut* who have disease progression following at least one line of ET including a CDK4/6i.

Clinical feedback is that in the UK, elacestrant will be used in a subpopulation of the marketing authorisation indication i.e. postmenopausal women, and men, with ER+/HER2-, locally advanced/mBC with an activating *ESR1-mut* following ≥12 months prior treatment with ET + CDK4/6i. The importance of duration of prior ET in determining the optimal treatment for these patients is supported by the ESMO Living Guidelines (2023), which provide a strong recommendation (category I A) for the use of elacestrant in patients with *ESR1*-mutated tumours who had long PFS on prior ET + CDK4/6i.[12]

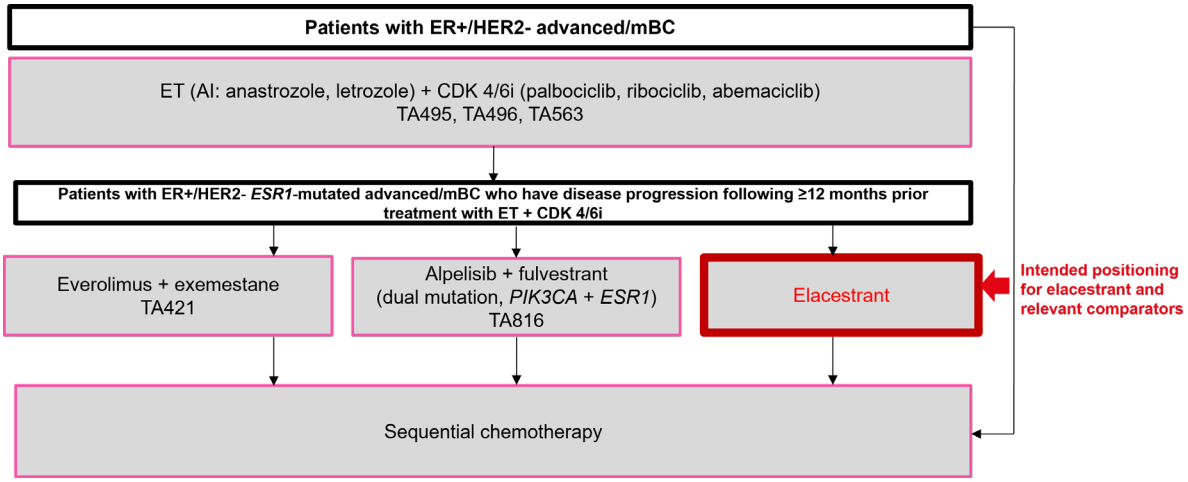
If chemotherapy is to be avoided, everolimus + exemestane is the most relevant comparator for elacestrant. Alpelisib + fulvestrant is a comparator for elacestrant for the subgroup of patients with ER+/HER2- advanced/mBC with both a *PIK3CA-mut* and an *ESR1-mut* (dual mutated population).

Based on UK clinical expert opinion, ET monotherapy and ET + chemotherapy are rarely used as treatment options for the population in this submission in clinical practice in England and Wales, and as such are not considered relevant comparators to elacestrant.[29] Chemotherapy is mainly reserved for patients with imminent risk of organ failure, and as such, chemotherapy is not considered a relevant comparator for elacestrant for the population in the submission.[12,77]

In a *post hoc* subgroup analysis of the pivotal phase III study (EMERALD), patients treated with elacestrant had a greater improvement in PFS with longer exposure (≥12 months) to prior ET + CDK4/6i (8.6 months) vs. ET monotherapy, 1.9 months.[28] The results of this *post hoc* subgroup analysis support the beneficial activity of elacestrant for patients with longer exposure (≥12 months) to prior ET + CDK4/6i.

The proposed place of elacestrant in the current treatment pathway in England and Wales is provided in Figure 6.

Figure 6: Proposed positioning of elacestrant in the current treatment pathway



Abbreviations: AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER+, oestrogen receptor-positive; *ESR1*, oestrogen receptor 1 gene; HER2-, human epidermal growth factor receptor 2-negative; mBC, metastatic breast cancer; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TA, technology appraisal

B.1.4 Equality considerations

There are no anticipated equality considerations for elacestrant.

B.2 Clinical effectiveness

EMERALD is the registrational, international, multicentre, randomised, open-label, active-controlled, event-driven, phase III trial of elacestrant vs. SOC, physicians' choice of fulvestrant, anastrozole, letrozole, or exemestane monotherapy.

- EMERALD enrolled patients with ER+/HER2-, advanced or mBC whose disease had relapsed or progressed following prior ET including a CDK4/6i.[33]
- EMERALD presents robust evidence in support of the marketing authorisation population for elacestrant in 228 patients with ER+/HER2-, locally advanced or mBC with an activating *ESR1-mut* who had disease progression following at least one line of ET including a CDK4/6i over a median follow up of 15.1 months.[33,98]

At the 6th September 2021 data cut-off (DCO), elacestrant demonstrated a statistically significant 45% reduction in the risk of progression or death vs. SOC in patients with *ESR1-mut*.

- Significant improvement in the primary efficacy endpoint (PFS per imaging review committee [IRC]) was observed for elacestrant vs. SOC, (HR: 0.55; 95% CI: 0.39 to 0.77, p=0.0005).[33,98,99]
- Similar results were reported in two *post hoc* subgroup analyses, which showed improvements in PFS for elacestrant vs. SOC for patients with *ESR1-mut* after ≥12 months of prior ET + CDK4/6i therapy (HR 0.410; 95% CI: 0.262 to 0.634, p <0.0001) and for patients with *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i (dual mutated population), (HR 0.423; 95% CI: 0.176 to 0.941).[28,30,100]

Landmark analyses and analyses of OS for the EMERALD trial supported the conclusion from the primary endpoint analysis in favouring elacestrant in patients with *ESR1-mut*.

- Landmark analysis demonstrated consistent clinical benefit for elacestrant vs. SOC in patients with *ESR1-mut* at all timepoints for PFS (3, 6, 12, and 18 months).[33,98,99] Landmark PFS analyses in the two *post hoc* subgroups also favoured elacestrant.[28,30,100,101]
- Whilst OS results were not significant, they favoured elacestrant at the interim analysis of OS (HR 0.59; 95% CI: 0.36 to 0.96, p=0.0325)[33,98] and the final analysis of OS (HR 0.903; 95% CI: 0.629 to 1.298, p=0.5823)[102] as did estimates of OS at various timepoints, consistent with the PFS landmark analyses. Landmark OS analyses in the two *post hoc* subgroups also favoured elacestrant.[28,30,100,101]

HRQoL was maintained between treatment groups in the EMERALD trial and over time.

- For the subgroup of patients with *ESR1-mut* who had received ≥12 months of prior ET + CDK4/6i, mean (standard deviation [SD]) EQ-5D-5L index scores at end of treatment (EOT) were similar for elacestrant [redacted] ([redacted]) and SOC [redacted] ([redacted]), with no notable differences over time. Similarly, there was no meaningful mean (SD) change from baseline for either elacestrant [redacted] ([redacted]) or SOC [redacted] ([redacted]).[100]

- For the subgroup of patients with *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i (dual mutated), mean (SD) EQ-5D-5L index scores at EOT were similar for elacestrant [redacted] ([redacted]) vs. SOC [redacted] ([redacted]), with no notable differences over time. Similarly, there was no meaningful mean (SD) change from baseline for either elacestrant [redacted] ([redacted]) or SOC [redacted] ([redacted]).[101]

During the treatment period in EMERALD, elacestrant showed a predictable and manageable safety profile similar to other ETs, that was consistent across all subgroups.

- AEs in both treatment arms were mainly Grades 1 and 2. The incidence of Grade 3 or 4 AEs was low in both treatment arms, with none exceeding 5%.[98]
- Among patients with *ESR1-mut*, there was a similar rate of treatment-emergent adverse events (TEAEs) reported with elacestrant and SOC, irrespective of relationship to trial therapy (105 [91.3%] for elacestrant and 92 [86.8%] for SOC). The four most common TEAEs reported for elacestrant were nausea (34.8%), arthralgia (20%), vomiting (18.3%) and fatigue (17.4%) vs. SOC (17.9%, 17.9%, 9.4% and 19.8%), respectively.[98]
- Among patients with *ESR1-mut*, the most common treatment-related adverse events (TRAEs) reported in both arms were nausea (22.6% vs. 12.3%) and fatigue (12.2% vs. 11.3%) for elacestrant vs. SOC, respectively.[98]
- Rates of TEAEs leading to dose reduction (5.2% vs. 0) and discontinuation (5.2% vs. 3.8%) were very low for both elacestrant and SOC, respectively, in patients with *ESR1-mut*.[98]
- There were 4 on-study deaths in patients with *ESR1-mut* (3 on elacestrant and 1 on SOC), none were treatment-related.[98]

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify relevant published evidence on the clinical efficacy and safety of therapies in patients with relapsed, recurrent, or advanced HR+, HER2-, BC having an *ESR1-mut* tumour who were exposed to prior ET + CDK4/6i in the advanced/metastatic setting. Based on recent ESMO treatment guidelines highlighting the importance of duration of CDK4/6i treatment on choice of treatment at progression,[12,77] a subgroup of particular interest is patients who have had a long response (received an average of ≥12 months of prior CDK4/6i treatment) on prior ET + CDK4/6i treatment. Both prospective and retrospective studies were included. The search was conducted on August 16th, 2023. Full details on the methodology and results of the SLR are provided in Appendix D.

One relevant randomised controlled trial (RCT) was identified (EMERALD) relating to the efficacy of elacestrant in patients with ER+/HER2-, advanced or mBC, with an activating *ESR1-mut*, whose disease has relapsed or progressed on at least one and no more than two lines of prior ET, including a CDK4/6i. EMERALD results are reported in 6 publications (3 publications, 3 congress abstracts) and unpublished data sourced from the clinical study report (CSR).[28,30,33,98,103–105] The EMERALD trial enrolled a total of 478 patients, 228 of whom

had an *ESR1-mut*, of whom 115 were treated with elacestrant and 113 with SOC (investigators choice of either fulvestrant, letrozole, anastrozole or exemestane monotherapy).

There are no targeted treatments specifically indicated for *ESR1*-mutated BC and in the absence of this, based on UK clinical feedback, the appropriate comparators for this appraisal are everolimus in combination with exemestane (TA421),[19] and for patients with both a *PIK3CA-mut* and *ESR1-mut* – alpelisib in combination with fulvestrant (per TA816).[20] Although these comparators are not specifically indicated in the *ESR1-mut* population, these are the treatments currently used in the post-CDK4/6i population in England and Wales. As there is no direct comparative evidence available between elacestrant and the relevant comparators from the pivotal EMERALD study, an indirect treatment comparison (ITC) is required to inform comparative efficacy in the post CDK4/6i and *ESR1-mut* population in the cost-effectiveness model for this appraisal.

The SLR identified only 2 studies (3 publications) relating to one of the appraisal comparators, the phosphatidylinositol 3 kinase (PI3K) inhibitor alpelisib (1 non-RCT [BYLieve, 2 publications] and 1 retrospective real-world cohort study [Raphael *et al.* 2022, 1 publication]),[54,106,107] however these publications only reported PFS data and did not include OS data, and PFS was not reported for *ESR1-mut* patients treated with ≥12 months of prior ET + CDK4/6i. No evidence was identified for everolimus in combination with exemestane in the specific population relevant to this appraisal (i.e. *ESR1-mut* and ≥12 months' prior ET including a CDK4/6i).

Due to no data being identified for the comparators, the company explored potential sources of real-world evidence (RWE). As the *ESR1-mut* is not currently tested for in the UK and as the mutations arise almost exclusively after previous exposure to ET in the metastatic setting, RWE sources outside the UK were explored. The decision was made to use an appropriate matching-adjusted indirect comparison (MAIC) to compare efficacy between elacestrant and comparators utilising RWE and the EMERALD study. Further details are provided in Section B.2.9.

B.2.2 List of relevant clinical effectiveness evidence

One RCT was identified that reported data on elacestrant: the phase III, open-label EMERALD trial. This was used to support the marketing authorisation of elacestrant and is used to inform the economic model (Table 6).

Table 6: Clinical effectiveness evidence

Study	EMERALD
Study design	Phase III, randomised, open-label, active-controlled, event-driven, multicentre trial
Population	Postmenopausal women and men with ER+/HER2-, advanced or mBC, whose disease has relapsed or progressed on at least one and no more than two lines of prior ET for advanced or mBC, which must have included a CDK4/6i in combination with fulvestrant or an AI. One chemotherapy regimen in the advanced/metastatic setting was permitted.

	In accordance with the marketing authorisation, the submission will focus on data from the pre-specified sub-group in patients with an activating *ESR1-mut.*
Intervention(s)	Elacestrant
Comparator(s)	Physician's choice of fulvestrant, anastrozole, letrozole, or exemestane monotherapy.
Indicate if study supports application for marketing authorisation	Marketing authorisation was granted by the MHRA on the 6th of December 2023 for KORSERDU® (elacestrant).
Indicate if study used in the economic model	Yes
Rationale for use/non-use in the model	EMERALD is the pivotal phase III trial in the relevant patient population and provides the primary evidence base for this submission.
Reported outcomes specified in the decision problem	• **PFS (imaging review committee-assessed)** • **OS** • Response rate (ORR, CBR and DOR, imaging review committee-assessed) • **AEs** • HRQoL (**EQ-5D-5L**, EORTC QLQ-C30 and PRO-CTCAE)
All other reported outcomes	• Safety and tolerability: SAEs, dose modifications, clinical laboratory parameters (i.e. haematology, chemistry, and coagulation), ECGs, ECOG performance status and vital signs) • Pharmacokinetics • Tumour assessments • Time to chemotherapy • Alterations in ctDNA relevant to ER+ BC and the CDK4/6 pathway and the relationship between these findings and clinical response • 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
Key publication	Bidard *et al. J Clin Oncol.* 2022;40(28):3246-3256l[33]
Secondary sources	• EMERALD CSR v.2 *Data on File*[98] • EMERALD SAP *Data on File*[108] • EMERALD OS Addendum to CSR v.2 *Data on File*[102] Cortés *et al.*, 2023[109] Bardia *et al.*, 2022[30] Bardia *et al.*, 2023[28] Dubash *et al.*, 2023[103] Aftimos *et al.*, 2022[104]

Abbreviations: AE, adverse event; AI, aromatase inhibitor; BC, breast cancer; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CSR, clinical study report; ctDNA, circulating tumour deoxyribonucleic acid; DOR, duration of response; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; ESMO, European Society of Medical Oncology; EQ-5D-5L, EuroQoL Five-dimension Five-level; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HRQoL, health-related quality of life; MHRA, Medicines and Healthcare products Regulatory Agency; ORR, objective response rate; OS, overall survival; PFS,

progression-free survival; PRO-CTCAE, Patient-Reported Outcome Common Terminology Criteria for Adverse Events; SAE, serious adverse event; SAP, statistical analysis plan; UK, United Kingdom
Source: Bidard (2022)[33], EMERALD CSR *Data on File* (2023)[98]

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Trial design

EMERALD was a phase III, international, multicentre, open-label, active-controlled, event-driven, RCT, including participants from the UK.[33,98] It was conducted across 228 sites in 17 countries (NCT03778931). Of the 478 patients who were enrolled, 228 had *ESR1-mut* (9 from the UK).[98]

Eligible patients were postmenopausal women, or men, aged 18 years or older, with histologically or cytologically proven ER+/HER2-, advanced or mBC with disease progression following one to two prior lines of ET for advanced or metastatic disease, which must have included a prior CDK4/6i in combination with ET.[33,98] Patients must have received no more than one line of cytotoxic chemotherapy for mBC.[33,98] Disease progression must have occurred during or within 28 days after treatment with one or two prior lines of ET for advanced or metastatic disease. Progression during or within 12 months of adjuvant ET was included as a line of ET for advanced or metastatic disease.[33,98] Further details of the study design and methodology can be found in Figure 7 and Table 7.

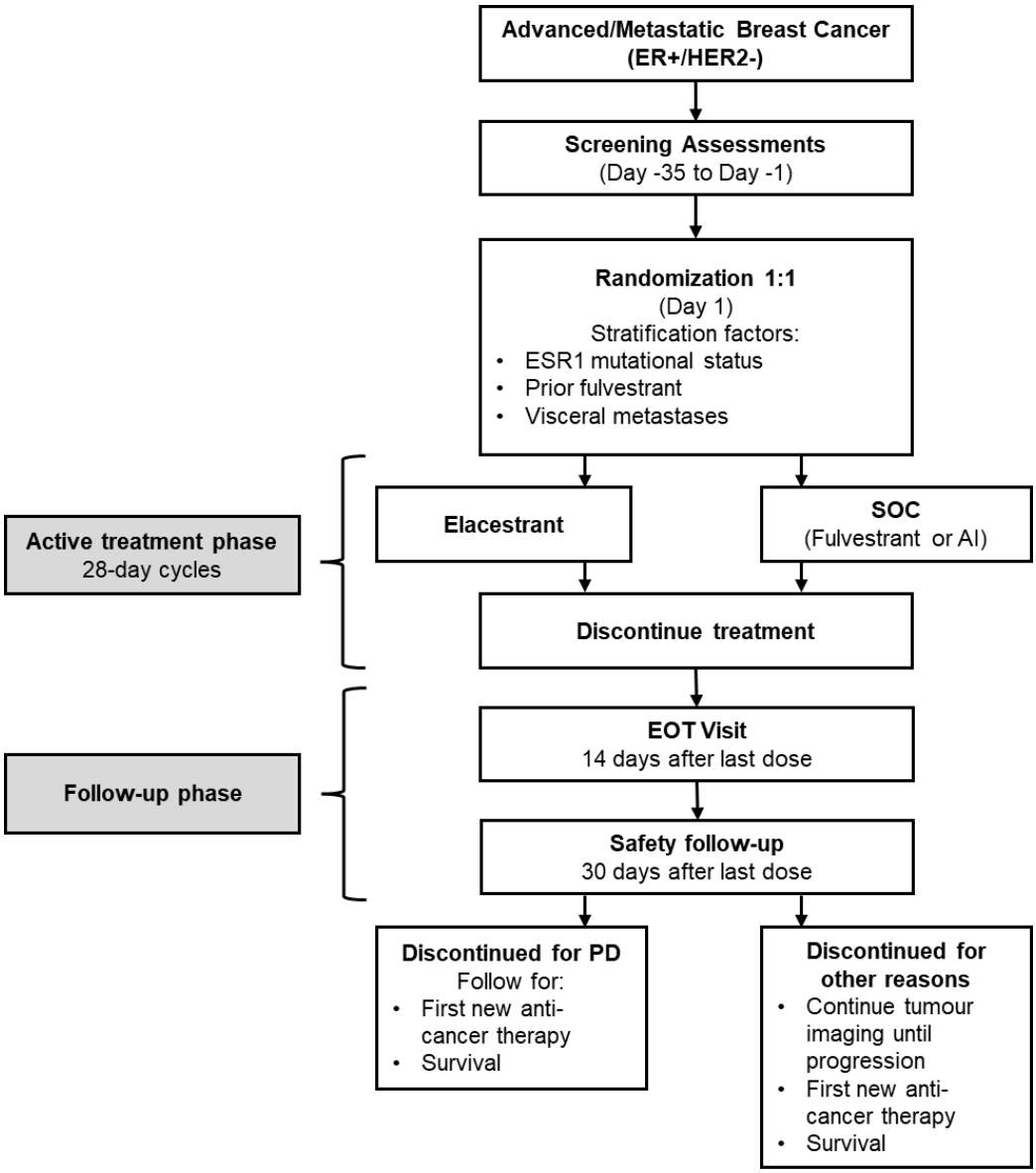
If patients met all the eligibility criteria, they were randomised 1:1 between elacestrant (n=115 patients with *ESR1-mut*) and SOC (n=113 patients with *ESR1-mut*).[33,98] Choice of SOC treatment was at the investigator's discretion and could be one of fulvestrant, anastrozole, letrozole, or exemestane monotherapy. Randomisation was conducted using Interactive Randomisation Technology (IRT), stratified according to prior treatment with fulvestrant (yes or no) or presence of visceral metastasis (yes or no) including lung, liver, brain, pleural and peritoneal metastasis.[33,98,108] Patients were also stratified by *ESR1-mut* status per ctDNA. As the UK MA is for this pre-specified *ESR1-mut* subgroup from EMERALD, only data for this subgroup are presented in this submission.

EMERALD had an active treatment phase, where patients received treatment in 28-day cycles.[98] Following the active treatment phase, patients who discontinued treatment due to disease progression entered a follow-up period during which survival data, the start date, and the name of the first new anti-cancer therapy were collected. For patients who discontinued treatment for reasons other than disease progression, death, consent withdrawal, toxicity, or loss to follow up and who did not begin new anti-cancer therapy, tumour assessments continued until disease progression, or the first new anti-cancer therapy was initiated. At that time, patients discontinued tumour assessments and continued to be monitored for survival data and the initiation of the first new anti-cancer therapy.[98]

Although the study was not blinded, efforts were made to minimise risk of bias; the sponsor personnel performing statistical analyses were blinded to treatment assignments and aggregated data by treatment assignment until after database lock, study/sponsor team members were blinded to aggregated data by treatment assignment until after database lock and an independent central IRC, blinded to patients' treatment assignment, reviewed radiographic images and clinical information collected on-study to determine the endpoints of disease response and progression (See Section B.2.5.1 for the risk of bias assessment of EMERALD).[98,108]

The primary efficacy endpoint was IRC-assessed PFS in All Patients and patients with *ESR1-mut*, using the truncated Hochberg procedure to adjust for the multiplicity of the primary endpoints and key secondary endpoint (OS).[33,98] The final PFS analysis was planned for when approximately 160 PFS events among the patients with *ESR1-mut* (340 events among All Patients) had occurred.[33,98] An interim survival analysis occurred at that timepoint, with a final survival analysis planned for when approximately 50% of patients had died, at which point the study would be considered complete.[98,110]

Figure 7: EMERALD | Study Design



Abbreviations: AI, aromatase inhibitor; EOT, end of treatment; ER, oestrogen receptor; *ESR1*, oestrogen receptor 1 gene; HER2, human epidermal growth factor receptor 2; PD, progressive disease; SOC, standard of care

Source: EMERALD CSR *Data on File* (2023)[98]

Table 7: Summary of EMERALD methodology

Trial name	EMERALD
Trial design[33,98]	Phase III, randomised, open-label, active-controlled, event-driven, multicentre trial. Patients were randomised 1:1 between elacestrant and SOC (physician's choice of fulvestrant, anastrozole, letrozole, or exemestane monotherapy). Stratification factors included *ESR1-mut* status (*ESR1-mut* vs. *ESR1-mut* nd), prior treatment with fulvestrant (yes or no) or presence of visceral metastasis (yes or no).
Duration of study[33,111]	10/05/2019 – 08/2024 (estimated)
Settings and locations where data were collected[98]	Multicentre study in 228 sites across 17 countries: Argentina, Australia, Austria, Belgium, Canada, Denmark, France, Greece, Hungary, Ireland, Israel, Italy, Portugal, South Korea, Spain, UK, and United States. Amongst patients with *ESR1-mut* (n=228), 9 were from the UK. UK recruitment sites included [redacted] (1 patient), [redacted] (1 patient), [redacted] (4 patients) and [redacted] (6 patients). An additional 3 UK patients were screened but not randomised.
Participant eligibility criteria[33,98]	**Key inclusion criteria** • Eligible patients were postmenopausal women, or men, aged 18 years or older with histologically or cytologically proven ER+/HER2- breast adenocarcinoma and either locally advanced disease not amenable to resection or radiation therapy with curative intent, or metastatic disease not amenable to curative therapy • Patients had to be appropriate candidates for endocrine monotherapy • ER and HER2- testing were performed by a local laboratory. ER positivity was defined as ≥1% staining by immunohistochemistry, with or without progesterone receptor positivity. HER2- negativity was defined according to current guidelines • Disease progression must have occurred during or within 28 days after treatment with one and no more than two prior lines of ET for advanced or metastatic disease. Progression on previous CDK4/6i treatment in combination with fulvestrant or an AI was required • Progression during or within 12 months of adjuvant ET was included as a line of ET for advanced or metastatic disease • One chemotherapy regimen in the advanced/metastatic setting was permitted • Progression during or within 28 days of completion of prior treatment with a CDK4/6i in combination with either fulvestrant or an AI in the metastatic setting o Prior treatment with a CDK4/6i not in combination with fulvestrant or an AI would not fulfil this criterion o Discontinuation of prior CDK4/6i due to toxicity, in the absence of progression, would not fulfil this criterion • ECOG performance status 0 or 1 and measurable disease per RECIST version 1.1 or evaluable bone-only disease with at least one lytic or mixed lytic-blastic bone lesion (blastic-only metastases not allowed)
	Key exclusion criteria • Prior treatment with elacestrant, GDC-0810, GDC-0927, GDC-9545, LSZ102, AZD9496, bazedoxifene, or other investigational SERD or investigational ER antagonist • Prior anti-cancer or investigational drug treatment if:

	○ Fulvestrant treatment <42 days before first dose of study drug Any ET <14 days before first dose of study drug (except for GnRH agonist therapy in male patients). ○ Chemotherapy or other anti-cancer therapy <21 days before first dose of study drug ○ Any investigational anti-cancer drug therapy <28 days or five half-lives (whichever is shorter) before the first dose of study drug. Enrolment of patients whose most recent therapy was an investigational agent should be discussed with the Sponsor ○ Bisphosphonates or RANKL inhibitors initiated or dose changed <3 months prior to first dose of study drug ○ Radiation therapy within 14 days before first dose of study drug (28 days for brain lesions) • Presence of symptomatic metastatic visceral disease defined in protocol • Intact uterus with a history of endometrial intraepithelial neoplasia • Diagnosis of any other malignancy within 5 years before enrolment (with some exceptions) • Any of the following cardiovascular events within 6 months of enrolment: severe/unstable angina, myocardial infarction, coronary/peripheral artery bypass graft, prolonged corrected QT interval Grade ≥2, uncontrolled atrial fibrillation, ongoing Grade ≥2 cardiac dysrhythmias, New York Heart Association Class II or greater heart failure, coagulopathy (thrombosis), and cerebrovascular accident (NB in the UK patients were excluded if they had a QTcF of ≥450 msec) • Child-Pugh Score greater than Class A • Coagulopathy or any history of coagulopathy within the past 6 months (with some exceptions) • Known bleeding disorder which could prohibit administration of fulvestrant • Known difficulty tolerating oral medications or conditions that would impair the absorption of oral medications • 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 • Major surgery <28 days before the first dose of study drug • Any concurrent severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase risk or interfere with compliance with the study • Known hypersensitivity to study drugs • Any contraindication, according to the respective PI or SmPC, for any of the SOC drug
Trial drugs[98]	**Intervention** Elacestrant dihydrochloride 400 mg/day (equivalent to elacestrant 345 mg)[28] once-daily oral dosing (protocol-defined dose reductions permitted to 300 mg or 200 mg daily). **Comparator** Investigator's choice of one of the following SOC ETs: • Fulvestrant: 500 mg administered intramuscularly on C1D1, C1D15, C2D1 and day 1 of every subsequent 28-day cycle • Anastrozole: 1 mg/day on a continuous dosing schedule • Letrozole: 2.5 mg/day on a continuous dosing schedule • Exemestane: 25 mg/day on a continuous dosing schedule

Concomitant medication[98]	**Permitted concomitant medication:** • Recorded if taken from 35 days prior to signing consent until 30 days after last dose of study drug • Could include oral, topical, intravaginal, rectal, inhaled, over-the-counter, herbal, supplements, vitamins, and substance use • Patients could receive supportive care agents to manage AEs and cancer symptoms (e.g. analgesics, heartburn medications, antiemetics, antidiarrheals) • If patient was receiving warfarin or other coumadin derivatives, INR or prothrombin time was to be monitored **Prohibited concomitant medication:** • All Patients: Hormonal medications or medications known to affect serum LH, FSH (excluding spironolactone) or oestrogen within 14 days of the first dose of study drug or any time within the study. Any systemic anti-cancer therapy or other chemotherapeutic agents. Bisphosphonates and RANKL inhibitors, unless the patient was on a stable dose for at least 3 months prior to the first dose of study drug. Surgical tumour resection, tumour embolisation and radiation therapy, unless the latter was for palliative pain management • Elacestrant group: Medications, herbal preparations, supplements, and herbs or foods known to be moderate/strong inhibitors or inducers of CYP3A • SOC group: Medications and supplements that are known to be strong inducers of CYP3A4 were not to be used/consumed for the duration of the study for patients taking exemestane. Otherwise, investigators were referred to the PI or SmPC
Primary outcome[33,98]	• PFS
Other outcomes used in the model/specified in scope[33,98]	• OS • Response rate (ORR, CBR and DOR) • AEs • HRQoL (EQ-5D-5L, EORTC QLQ-C30 and PRO-CTCAE)[109]
Other outcomes of interest[98]	• Safety and tolerability: SAEs, dose modifications, clinical laboratory parameters (i.e. haematology, chemistry, and coagulation), ECGs, ECOG performance status and vital signs) • Pharmacokinetics • Tumour assessments • Time to chemotherapy
Pre-planned subgroups[98,108]	• Subgroup analyses of IRC-assessed PFS, OS, ORR, DOR, CBR and PROs will be performed in the same manner as the analyses using the ITT population for patients with *ESR1-mut* and for All Patients (those with *ESR1-mut* and without) for the following stratification factors: • Prior treatment with fulvestrant (yes/no) • Presence of visceral metastases (yes/no) • For the analyses of All Patients, stratification factors include *ESR1*-mutational status (*ESR1-mut* vs. no detectable *ESR1-mut*) • For the following subgroups: • Age group • Race • Region

	• Baseline ECOG performance status • Measurable disease at baseline • Number of prior lines of ET in advanced/metastatic setting • Number of lines of chemotherapy in the advanced/metastatic setting
***Post hoc* subgroups**	• Patients who received study drug following ≥12 months on a prior ET + CDK4/6i[28,30,100] • Dual mutated *ESR1* and *PIK3CA* patients[28,101]

Abbreviations: AE, adverse event; AI, aromatase inhibitor; C, cycle; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CYP3A4, cytochrome P450 3A4; D, day; DOR, duration of response; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D-5L, EuroQoL Five-dimension Five-level; ER, oestrogen receptor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; FSH, follicle stimulating hormone; GnRH, gonadotropin-releasing hormone; HER2, human epidermal growth factor receptor 2; HRQoL, health-related quality of life; INR, international normalised ratio; IRC, imaging review committee; ITT, intention-to-treat; LH, luteinizing hormone; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PI, product insert; *PIK3CA*, phosphatidylinositol 3 kinase; PRO, patient-reported outcome; PRO-CTCAE, Patient-Reported Outcome Common Terminology Criteria for Adverse Events; QTcF, QT corrected for heart rate by Fridericia's cube root formula; RANKL, receptor activator of nuclear factor kappa-B; RECIST, response evaluation criteria in solid tumours; SAE, serious adverse event; SERD, selective oestrogen receptor degrader; SmPC, Summary of Product Characteristics; SOC, standard of care; UK, United Kingdom

Source: Bidard (2022)[33], ClinicalTrials.gov[111]; EMERALD CSR *Data on File* (2023)[98]; EMERALD SAP *Data on File*[108]

B.2.3.1.1 Trial endpoints

Trial endpoints, their definitions, and censoring rules are shown in Table 8.

Table 8: EMERALD | Summary of key endpoints

Endpoint/ assessment	Definition[98,108]	Timing of assessments and follow-up[98,108]	Censoring rules[98,108]
Primary endpoint (in patients with *ESR1-mut* and All Patients)			
IRC-assessed PFS[33]	Length of time from randomisation until the date of objective disease progression per RECIST version 1.1 or death from any cause	Tumour assessments were performed every 8 weeks (± 7 days) from randomisation in the active treatment phase of the study and at the EOT (≤14 days from last dose) If bone lesions were identified at screening, patients had radionucleotide bone scans or whole-body MRI every 24 weeks (± 7 days) from randomisation, at confirmation of a CR and at the EOT (≤14 days from last dose) These assessments were performed until radiographically and/or clinically documented disease progression as per RECIST version 1.1, initiation of new anti-cancer therapy, or discontinuation from study participation If treatment discontinued for a reason other than disease progression, tumour assessments were performed every 8 weeks (± 7 days) in the follow-up period and bone scans or whole-body MRI as clinically indicated and/or every 24 weeks (± 7 days) until disease progression, initiation of the first new anti-cancer therapy, or discontinuation from overall study participation	Patients without objective disease progression or death: 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 Censored progression or death after missing ≥2 consecutive post-baseline tumour assessments: on date of last tumour assessment before missed assessments or date of randomisation, whichever is later Censored progression or death after taking new anti-cancer therapies: at the date of last adequate tumour assessment before or on initiation of new systemic anti-cancer therapy Lost to follow-up or withdrew consent before documented progression or death: by date of last adequate tumour assessment No baseline measurable or evaluable lesion: from date of randomisation No post-baseline assessments and no death: from date of randomisation

Key secondary endpoint (in patients with *ESR1-mut* and All Patients)			
OS[33]	Length of time from randomisation until the date of death from any cause	As above for IRC-assessed PFS Patients no longer undergoing tumour evaluations were to continue to be monitored every 8 weeks for survival and the initiation of the first new anti-cancer therapy Follow-up finished at the time of the final OS analysis when approximately 50% of patients in the study had died	Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive. Reasons for censoring included: ○ Still in survival follow-up ○ Terminated prior to death ○ Lost to follow-up ○ Withdrawn consent ○ Other
Secondary endpoints (in patients without detectable *ESR1-mut*)			
IRC-assessed PFS-[33]	Length of time from randomisation until the date of objective disease progression per RECIST version 1.1 or death from any cause	As above for IRC-assessed PFS	As above for IRC-assessed PFS
OS[33]	Length of time from randomisation until the date of death from any cause	As above for key secondary endpoint OS	As above for key secondary endpoint OS
Secondary endpoints (in *ESR1-mut*, patients without detectable *ESR1-mut* and All Patients)			
ORR (IRC-assessed)[33]	Percentage of patients with measurable disease who had achieved either a confirmed CR or PR per RECIST v1.1	As above for IRC-assessed PFS	Not applicable
CBR (IRC-assessed)[33]	Percentage of patients who had achieved either a confirmed CR or PR or stable disease at ≥24 weeks from randomisation per RECIST v 1.1	As above for IRC-assessed PFS	Not applicable

DOR (IRC-assessed)[33]	Duration of time from the date when criteria are met for either a CR or PR (whichever is first recorded) per RECIST v1.1 until the first date that recurrent or PD is objectively documented, or death from any cause	As above for IRC-assessed PFS	DOR will be censored at the last assessment if the patient did not have disease progression If patients receive new systemic anti-cancer therapy before progression, DOR will be censored at the last assessment before or on the date of initiation of new systemic anti-cancer therapy Patients who had PD or death after ≥2 missing tumour assessments will be censored at the last tumour assessments prior to the missed visits
Secondary Endpoints (in patients with *ESR1-mut* and All Patients)			
Safety and tolerability[33]	AEs: deemed treatment related if they occurred after the first dose of study drug and ≤30 days after the last dose of study drug SAEs led to death, hospitalisation, or prolonged hospitalisation, persistent or significant incapacity or disruption to normal daily life, congenital anomaly/birth defect, were life-threatening or required intervention to avoid one of the above Dose modifications Clinical laboratory parameters, ECGs, ECOG performance status, and vital signs	Safety assessments were planned to be made at the study site at scheduled study visits Study assessments included:[a] ○ Laboratory tests (chemistry, haematology, coagulation): screening, C1D1, C1D15 (± 2 days), D1 of subsequent cycles (± 2 days), EOT (+ 14 days) ○ ECGs: screening, C1D1, C1D15 (± 2 days), D1 of subsequent cycles (± 2 days) though to C4 then D1 of every other cycle thereafter starting with C6, EOT (+ 14 days) ○ Physical examinations: screening, C1D1, D1 of subsequent cycles (± 2 days), EOT (+ 14 days) ○ ECOG performance status: screening, C1D1, D1 of subsequent cycles (± 2 days), EOT (+ 14 days)	Not applicable

		○ Vital signs: screening, C1D1, C1D15 (± 2 days), D1 of subsequent cycles (± 2 days), EOT (+ 14 days) Followed up until 30 days post treatment or until resolution or stabilisation of all TRAEs to either ≤Grade 2 or baseline, whichever was longer, or until the patient was lost to follow-up	
Pharmacokinetics[98,108]	Evaluation of elacestrant concentrations at pre-dose and 4 hours post-dose on C1D1, pre-dose trough concentration (C_{trough}) and 4 hours post-dose on C1D15, and pre-dose (C_{trough}) on C2D1	Blood samples for PK were collected on C1D1, C1D15 (± 2 days), C2D1(± 2 days) for the patients randomised to the elacestrant group only +/- when AEs or SAEs occurred	Not applicable
PRO endpoints[98,108]	Assessed using HRQoL scales EQ-5D-5L, EORTC QLQ-C30 and PRO-CTCAE	Patients completed these at the start of the visit, prior to other assessments and prior to significant interactions between patient and staff using electronic tablets ○ Schedule: C1D1, C1D15 (± 2 days), C2D1 D1 of subsequent cycles (± 2 days) up to C4 then D1 of every other cycle starting with C6, EOT (+ 14 days) and at the post treatment safety follow-up visit 30 days after last dose of study drug (± 3 days)	Not applicable
Exploratory endpoints (*ESR1-mut*, patients without detectable *ESR1-mut* and All Patients)			
Time to chemotherapy[98,108]	Time from randomisation to initiation of chemotherapy	Not applicable	Not applicable

Footnotes: [a]Chemistry included BUN or urea, creatinine, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, magnesium, albumin, total protein, total bilirubin (direct and indirect if total is > ULN), alkaline phosphatase, ALT, AST, glucose and lipid panel (total cholesterol, LDL, HDL, and triglycerides). Haematology included hemoglobin, hematocrit, white blood cell count with differential (including absolute neutrophil count, lymphocyte, monocyte, eosinophil, and basophil counts), and platelet count. Coagulation tests included prothrombin time or INR (per the site standards), aPTT (PTT was allowed if aPTT was not available), and fibrinogen. Physical examination at screening included total body examination of general appearance, skin, neck (including thyroid), ears, eyes, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and a clinical neurological examination. Post-screening physical examinations were targeted based on findings present at screening. Vital signs included

temperature, respiratory rate, sitting blood pressure, and sitting pulse rate.
Abbreviations: AE, adverse event; BC, breast cancer; C, cycle; CBR, clinical benefit rate; CDK4/6i, cyclin dependent kinase 4/6 inhibitor; CR, complete response; D, day; DOR, duration of response; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EOT, end of treatment; EQ-5D-5L, EuroQoL Five-dimension Five-level; ER, oestrogen receptor; *ESR1*, oestrogen receptor 1 gene; HRQoL, health-related quality of life; IRC, imaging review committee; MRI, magnetic resonance imaging; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetic(s); PR, partial response; PRO, patient-reported outcomes; PRO-CTCAE, Patient-Reported Outcome Common Terminology Criteria for Adverse Events; RECIST, response evaluation criteria in solid tumours; SAE, serious adverse event
Source: Bidard (2022)[33] , EMERALD CSR *Data on File* (2023)[98], EMERALD SAP *Data on File*[108]

B.2.3.1.2 Baseline demographic and disease characteristics

Patient baseline demographic and disease characteristics for patients with *ESR1-mut* in EMERALD are presented in Table 9. Groups were well balanced with respect to all baseline disease and demographic characteristics.

The median age was 64 years for elacestrant and 63 years for SOC. There were no males in the *ESR1-mut* subgroup, or in either treatment group, and all female patients were postmenopausal. None of the patients had an ECOG performance status of >1. Most patients were white, but otherwise race or ethnicity were well balanced across the different treatment groups.[33]

Visceral metastases were present in 165 (72.4%) of the patients with *ESR1-mut*,[33] with the most common sites being bone (195 [85.5%]), liver (125 [54.8%]), lymph nodes (61 [26.8%]), lung (58 [25.4%]) and breast (45 [19.7%]). During the study, 3 patients with *ESR1-mut* were discovered to have been mis-stratified due to not having an *ESR1-mut*.[98]

Most patients with *ESR1-mut* (151 [66.2%]) had ductal tumour histology (74 [64.3%] in the elacestrant group and 77 [68.1%] in the SOC group).[98]

Consistent with the inclusion criteria, all patients had prior ET + CDK4/6i therapy, at most 1 line of chemotherapy for advanced/metastatic disease and either 1 or 2 lines of ET in the advanced or metastatic setting. For patients with *ESR1-mut*, prior ET in any setting was reported for 112 patients in the elacestrant group and 109 patients in the SOC group.[33] The median duration of ET was 24 months (range, 2 to 164 months) in the elacestrant group and 23.8 months (2 to 149 months) in the SOC group.[98]

Table 9: EMERALD | Baseline characteristics | All patients with *ESR1-mut*

	Patients with *ESR1-mut*	
Characteristic	**Elacestrant N=115**	**SOC N=113**
Median age, years (range)	64.0 (28–89)	63.0 (32–83)
Female, n (%)	115 (100)	113 (100)
Race (patients could select >1) or ethnicity, n (%)		
White	84 (89.4)	80 (87)
Asian	5 (5.3)	8 (8.7)
Black or African American	4 (4.3)	4 (4.3)
Other	1 (1.1)	0 (0.0)
Hispanic	10 (8.7)	10 (8.8)
ECOG performance status, n (%)		
0	67 (58.3)	62 (54.9)

1	48 (41.7)	51 (45.1)
>1	0 (0.0)	0 (0.0)
Visceral metastasis[a], n (%)	81 (70.4)	84 (74.3)
Prior adjuvant therapy, n (%)	62 (53.9)	65 (57.5)
Prior therapies for advanced or metastatic disease, n (%)		
Prior CDK4/6i	115 (100)	113 (100)
Any prior ET[b]	112 (97.4)	109 (96.5)
Fulvestrant	27 (23.5)	28 (24.8)
AI	101 (87.8)	96 (85.0)
Tamoxifen	9 (7.8)	9 (8.0)
mTOR inhibitor	6 (5.2)	3 (2.7)
PI3K inhibitor	1 (0.9)	0 (0.0)
No. of prior lines of ET in the advanced or metastatic setting, n (%)		
1	73 (63.5)	69 (61.1)
2	42 (36.5)	44 (38.9)
No. of prior lines of chemotherapy in the advanced or metastatic setting, n (%)		
0	89 (77.4)	81 (71.7)
1	26 (22.6)	32 (28.3)

Footnotes: [a]Includes lung, liver, brain, pleural, and peritoneal involvement; [b]Remaining patients progressed during or within 12 months of adjuvant endocrine therapy

Abbreviations: AI, aromatase inhibitor; CDK4/6i, cyclin dependent kinase 4/6 inhibitor; ECOG, Eastern Cooperative Oncology Group; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; mTOR, mammalian target of rapamycin; n, number; PI3K, phosphatidylinositol 3 kinase; SOC, standard of care

Source: Bidard (2022),[33] EMERALD CSR *Data on File* (2023)[98]

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Analysis sets

Nine populations were included in the analysis in EMERALD, as described in Table 10. Efficacy analyses were performed on the intention-to-treat (ITT), response evaluable (RE) and clinical benefit evaluable (CBE) populations, and safety analyses on the safety analysis set (unless otherwise stated). Regarding analysis, each individual population included in the primary efficacy analysis (All Patients and patients with *ESR1-mut*) were counted as distinct analysis populations e.g. there was an ITT for All Patients and an ITT for patients with *ESR1-mut* (Table 10).

Table 10: EMERALD | Overview of analysis sets

Analysis set population	Definition[98,108]	Endpoints	All Patients, n (%)[98]		Patients with *ESR1-mut*, n (%)[98]	
			Elacestrant N=239	SOC N=239	Elacestrant N=115	SOC N=113
ITT	All randomised patients	PFS, OS and HRQoL	239 (100)	239 (100)	115 (100)	113 (100)
Per-protocol	All those randomised except for patients who had a major protocol deviation	Sensitivity analyses for PFS if primary endpoints are statistically significant	234 (97.7)	230 (96.2)	115 (100)	106 (93.8)
Modified per-protocol			233 (97.5)	228 (95.4)	114 (99.1)	105 (92.9)
Safety	All patients who received at least 1 dose of study drug	Safety analyses	237 (99.2)	230 (96.2)	115 (100)	106 (93.8)

IRC-assessed response evaluable (RE)	Includes all randomised patients who had measurable disease (i.e. at least 1 target lesion) at baseline and at least 1 post-baseline RECIST assessment on any (target or non-target) lesions and/or had a new lesion assessed by IRC or PI	ORR, DOR	179 (74.9)	182 (76.2)	85 (73.9)	86 (76.1)
PI-assessed RE		ORR. DOR	189 (79.1)	192 (80.3)	91 (79.1)	92 (81.4)
IRC-assessed clinical benefit evaluable (CBE)	Includes all randomised patients who had measurable and/or evaluable disease (i.e. target and/or non-target lesions) at baseline and at least 1 post-baseline RECIST assessment on any (target or non-target) lesions and/or had a new lesion assessed by IRC or PI	CBR	228 (95.4)	215 (90.0)	108 (93.9)	104 (92.0)
PI-assessed CBE		CBR	228 (95.4)	212 (88.7)	108 (93.9)	100 (88.5)
Pharmacokinetic	Includes all patients who received at least 1 dose of elacestrant and have PK concentration data for at least 1 scheduled time point	PK analyses	236 (98.7)	NA	114 (99.1)	NA

Footnotes: In the Bidard 2022 publication, the ITT population for SOC was n=238 because a patient enrolled in the SOC arm relocated and was missed during the initial analysis – the PFS estimates (medians, HRs etc) were not impacted and *ESR1-mut* population numbers were not impacted.
Abbreviations: CBE, clinical benefit evaluable; CBR, clinical benefit rate; DOR, duration of response; HRQoL, health-related quality of life; IRC, imaging review committee; ITT, intention-to-treat; NA, not assessed; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PI, principal investigator; PK, pharmacokinetic; RE, response evaluable; RECIST, response evaluation criteria in solid tumours; SOC, standard of care
Source: EMERALD SAP *Data on File*[108]*;* EMERALD CSR *Data on File* (2023)[98]

B.2.4.2 Statistical analyses

Statistical methods are summarised in Table 11.

Table 11: EMERALD | Summary of statistical analyses

Hypothesis objective	The null hypothesis for the primary endpoint in patients with *ESR1-mut* is that elacestrant does not differ from the SOC treatment group in the IRC-assessed PFS; the alternative hypothesis is that elacestrant differs from the SOC treatment group in the IRC-assessed PFS.
Statistical analysis	**General methods:** For continuous variables, descriptive statistics included the number of patients, mean, standard deviation, median, Q1, Q3, minimum, and maximum. For categorical variables, descriptive statistics included the number of patients, frequency counts and percentages. Time-to-event endpoints were analysed by the Kaplan–Meier method. Data from all sites were pooled for all analyses unless otherwise specified. Randomisation stratification factors for the *ESR1-mut* subgroup included prior treatment with fulvestrant (yes vs. no) and presence of visceral metastases (yes vs. no).[98,108] **Primary endpoint: IRC-assessed PFS**[98,108] The final analysis of PFS was planned for when approximately 160 events of objective disease progression or death based on IRC assessment had occurred among patients with *ESR1-mut* (340 events among All Patients). Analysis was based on the ITT population (both for All Patients and patients with *ESR1-mut*) and used the truncated Hochberg procedure to adjust for the multiplicity of the primary endpoints and the key secondary endpoint (OS). Results were summarised by treatment group with median (95% CI), Q1 and Q3 (95% CI), and PFS rates (95% CIs) at 3, 6, 12 and 18 months. The difference in primary endpoints between the two treatment groups were analysed using the stratified log-rank test with the randomisation stratification factors for generation of the p-value. The HR and 95% CI for the treatment effect were estimated using the stratified Cox proportional hazards regression model with Effron method of handling ties, stratified by randomisation stratification factors. CIs were constructed using the profile likelihood method. The analyses were performed using Kaplan–Meier methods and displayed graphically with median event times and 95% CIs. CIs were constructed using the method of Brookmeyer and Crowley via linear transformation. Two sensitivity analyses were performed in the same manner as the primary efficacy analyses and included 'events' as those that were recorded after missing 2 or more consecutive tumour assessments where; 'actual event PFS analysis' defined the event date as the actual event date after the 2 missed tumour assessments and the 'backdating PFS analysis' defined the event date as the date of the next scheduled tumour assessment after the last adequate tumour assessment. One sensitivity analysis (unstratified analysis) assessed the impact of stratification and compared the two treatment groups using an unstratified log-rank test, presenting the HR and 95% CI obtained using the unstratified Cox regression model. The final sensitivity analysis used the Per Protocol population in the same manner as the primary efficacy analysis if the primary endpoints were statistically significant.[98,108] **Key secondary endpoint: OS**[98,108] OS was analysed based on the ITT population (both for All Patients and patients with *ESR1-mut*) in a similar manner to the primary PFS analysis. An interim analysis was performed at the time of the primary PFS analysis. A final analysis of OS was performed after the pre-specified number of events of 245

	(51%) as per the protocol.[102] Results were summarised by treatment group with median OS (95% CI), Q1 and Q3 (95% CI), and OS rates (95% CIs) at 6, 12, 18 and 24 months. OS was analysed using the Kaplan–Meier method and displayed graphically, with median event times and 95% CIs displayed. The HR and 95% CI were estimated using the Cox regression model. The difference between treatment groups was analysed using the stratified log-rank test with the randomisation stratification factors for generation of p-value. A truncated Hochberg procedure was used to test the primary end points. Given that both primary end points were met, an alpha of .05 was passed to OS.[33] A 2-sided alpha level of 0.01% was allocated at the primary PFS analysis time point and a 2-sided alpha level of 4.99% was allocated at the final OS analysis timepoint.[108] Sensitivity analyses were performed to examine censoring patterns to rule out attrition bias with regard to the treatment comparisons, duration of follow up using medians (time from randomisation to date of death or to date of censoring for censored patients either for all patients or by treatment group).[108] **Other secondary endpoints** **IRC-assessed PFS and OS in patients without detectable *ESR1-mut*** Performed in the same manner as the analyses of the primary and key secondary efficacy endpoints respectively.[98,108] **IRC assessed response:** ○ The ORR will be summarized as a binomial response rate with 95% CIs based on Clopper-Pearson method using the RE population (both for All Patients and patients with *ESR1-mut*). Comparison between treatment groups will be performed using Cochran-Mantel-Haenszel test adjusting for randomisation stratification factors. The Mantel-Fleiss criterion will be checked to verify the suitability of CMH test. If Mantel-Fleiss criterion ≤5 (which might happen with many small strata), an exact test (Proc Logistic) will be used instead with adjustment for the same set of randomization stratification factors. Difference between treatment groups in the ORR along with 95% stratified Newcombe confidence limits for CI will also be provided.[98,108] ○ DOR was summarised using the RE population (both for All Patients and patients with *ESR1-mut*).[98,108] DOR was analysed by treatment group using the Kaplan–Meier method, with the median, 25th and 75th percentiles reported along with the 95% CIs. The Kaplan–Meier curve was also plotted by treatment group.[108] ○ CBR using the CBE population (both for All Patients and patients with *ESR1-mut*) was analysed in the same manner as the analysis of ORR.[98,108] **PRO outcomes**: the EQ-5D-5L, EORTC QLQ-C30 and the PRO-CTCAE were used, with results summarised by treatment group and based on the ITT population (both for All Patients and patients with *ESR1-mut*). Sensitivity analyses were performed for all PRO endpoints by excluding patients who had at least 1 missing visit due to COVID-19, in the same manner as the primary PRO analyses. PRO endpoints values and changes from baseline were summarised by treatment group.[98,108] ○ The EQ-5D-5L explored the impact of treatment and disease state on health state utility. The EQ-5D profile was converted into a weighted health state utility value (EQ-5D index) by applying a country-specific equation that represents the comparative value of health state (based on nation valuation sets, or a crosswalk algorithm if not available). Descriptive statistics were calculated for each scheduled visit/time point in the study, for each study drug and as a total. For the EQ-5D index and EQ-VAS, summary statistics (n, mean, median, SD, min and max), and change from baseline were reported.[108]

	○ For the EORTC QLQ-C30, QoL endpoints were summarised by treatment at baseline and each study visit, along with change from baseline. Line graph presentation of mean (±SD) plots of scores and change from baseline vs. time point were produced. Summaries of absolute and change from baseline values of each EORTC QLQ-C30 scale/item and associated 95% CI were reported by scheduled visit for each treatment group. Line graph presentation of least square mean plots of scores versus time point were produced.[108] ○ PRO-CTCAE data at baseline were presented as the number (%) of patients with each level of attribute item for each PRO-CTCAE symptom term. Change from baseline at all visits were presented in 3 categories: improved, no change or worsened from baseline for each PRO-CTCAE symptom term. A bar chart of the incidence by visit was presented for each symptom term.[108] ○ A mixed model repeated measures model was developed to analyse change from baseline of QoL over study visits through to cycle 6.[108] Subgroup analyses were performed for the IRC-assessed PFS, OS, ORR, DOR, CBR and PROs with the same stratification factors as the primary analysis for 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 ECOG Performance Status (0 vs. 1), measurable disease at baseline (yes vs. no), number of prior lines of ET in the advanced/metastatic setting (1 vs. 2) and number of lines of chemotherapy in the advanced/metastatic setting (0 vs. 1).[98,108] **Safety:** Analysed using the safety population (both for All Patients and patients with *ESR1-mut*). AEs were summarised by patient incidence rates; therefore, in any tabulation, a patient contributed only once to the count for a given system organ class or preferred term. Preferred terms for a similar medical concept (i.e. synonym terms) across different system organ classes were grouped together in all AE summary tables, except as otherwise noted. All listings presented preferred terms by original term. For summaries by severity/toxicity grade, a patient with multiple occurrences under the same preferred term or system organ class was represented under the most severe occurrence. For summaries by relationship to study drug, a patient with multiple occurrences under the same preferred term or system organ class was represented under the most related occurrence. The worst toxicity grade per patient, by system organ class or per preferred term was used in the CTCAE grade summary. Missing grade and missing relationship to study drug were not imputed.[98,108] In the case of multiple observations at a specific visit, the latest observation was used. If more than 1 observation was made on the same day, an average value (if continuous) or the worst value (if categorical) was included in the analysis.[98,108] **Pharmacokinetic evaluations**: Elacestrant plasma concentrations were summarised descriptively (with n, mean, SD, coefficient variation, median, minimum, maximum, geometric mean and its associated coefficient variation), by visit and nominal timepoint. Plots of geometric means by nominal timepoint were produced.[98,108] **Time to chemotherapy:** Summarised descriptively, by treatment group, for the patients who received chemotherapy as first systemic therapy after treatment discontinuation.[98,108]
Sample size, power calculation	The primary endpoint of the study was PFS. It was estimated that 220 patients with an *ESR1-mut* would need to be enrolled to enable the required 160 PFS events to be reached to provide 80% power to detect an HR of 0.610 at the two-sided alpha level of 2.5%.[33,98,108] The sample size calculation assumed a median PFS of 5.3 months for the SOC treatment group and 8.7 months for the elacestrant group,[98,108] and was based on available data at that time related to the efficacy of fulvestrant as a

	second/third-line treatment. The effect of prior CDK4/6i exposure on the activity of fulvestrant was not known at the time this study was initiated. These recent data clearly showed that prior therapy with CDK4/6i decreases response/PFS to subsequent single agent ET.[112] The 2-sided alpha level of 2.5% for the sample size calculation ensured that at least 1 of the 2 primary efficacy endpoints passed the Hochberg procedure to control the overall alpha level at 5.0%. Based on the enrolment of 228 patients with *ESR1-mut*, and the assumption that approximately 114 OS events would occur by the final analysis, the study would have 39% power to detect an HR of 0.73 at a 1-sided alpha level of 2.5%. Assuming median OS of 28 months for SOC, this gave a median OS of 38 months for elacestrant and accounts for interim analysis and alpha spending equal to 0.0001.[98] Other efficacy end points were analysed without adjustment for p-values at the two-sided alpha level of .05.[33,108]
Data management, patient withdrawals	Patients were able to withdraw from the study at any time and the reason was documented in the patient's medical records and entered into the End of Study electronic Case Report Form (eCRF). If possible, EOT assessments were completed unless the patient had withdrawn consent.[98,108] When tabulating categorical data, "missing" was included as a category and the number of patients with missing data presented.[98,108]
Statistical analysis timepoints	For PFS, final analysis was planned to be performed after approximately 160 PFS events for patients with *ESR1-mut* or 340 PFS events for All Patients.[33,98,108] However, the final PFS analysis was conducted when there were 140 and 300 events, respectively.[98] A pre-specified interim OS analysis occurred at the time of the final PFS analysis with an allocated two-sided alpha level of 0.0001 according to the Haybittle-Peto rule. For OS, the final analysis occurred at the pre-specified number of events of 245 (51%) as per the protocol.[102]

Abbreviations: CBR, clinical benefit rate; CBE, clinical benefit evaluable; CI, confidence interval; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EOT, end of treatment; EQ-5D-5L, EuroQoL Five-dimension Five-level; EQ-VAS, EuroQol visual analogue scale; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; HR, hazard ratio; IRC, imaging review committee; ITT, intention-to-treat; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; PRO-CTCAE, Patient-Reported Outcome Common Terminology Criteria for Adverse Events; PFS, progression-free survival; Q, quartile; QoL, quality of life; RE, response evaluable; SD, standard deviation; SOC, standard of care

Source: Bidard (2022)[33], EMERALD SAP *Data on File*[108], EMERALD CSR *Data on File* (2023)[98]

B.2.4.3 Patient flow in EMERALD

For full details of the participant flow in EMERALD, see Appendix D. Of the 695 patients who were screened, 478 (68.8%) were randomised to either elacestrant (n=239) or SOC (n=239). In the Bidard 2022 publication,[33] this number is 477 because a patient enrolled in the SOC arm relocated and was missed during the initial analysis – the PFS estimates (medians, HRs etc) were not impacted. Reasons for exclusion of the 217 (31.2%) patients who did not pass screening included ineligibility (204 [29.4%]), withdrawn consent (10 [1.4%]), investigator decision (2 [0.3%]) and significant noncompliance (1 [0.1%]).[98]

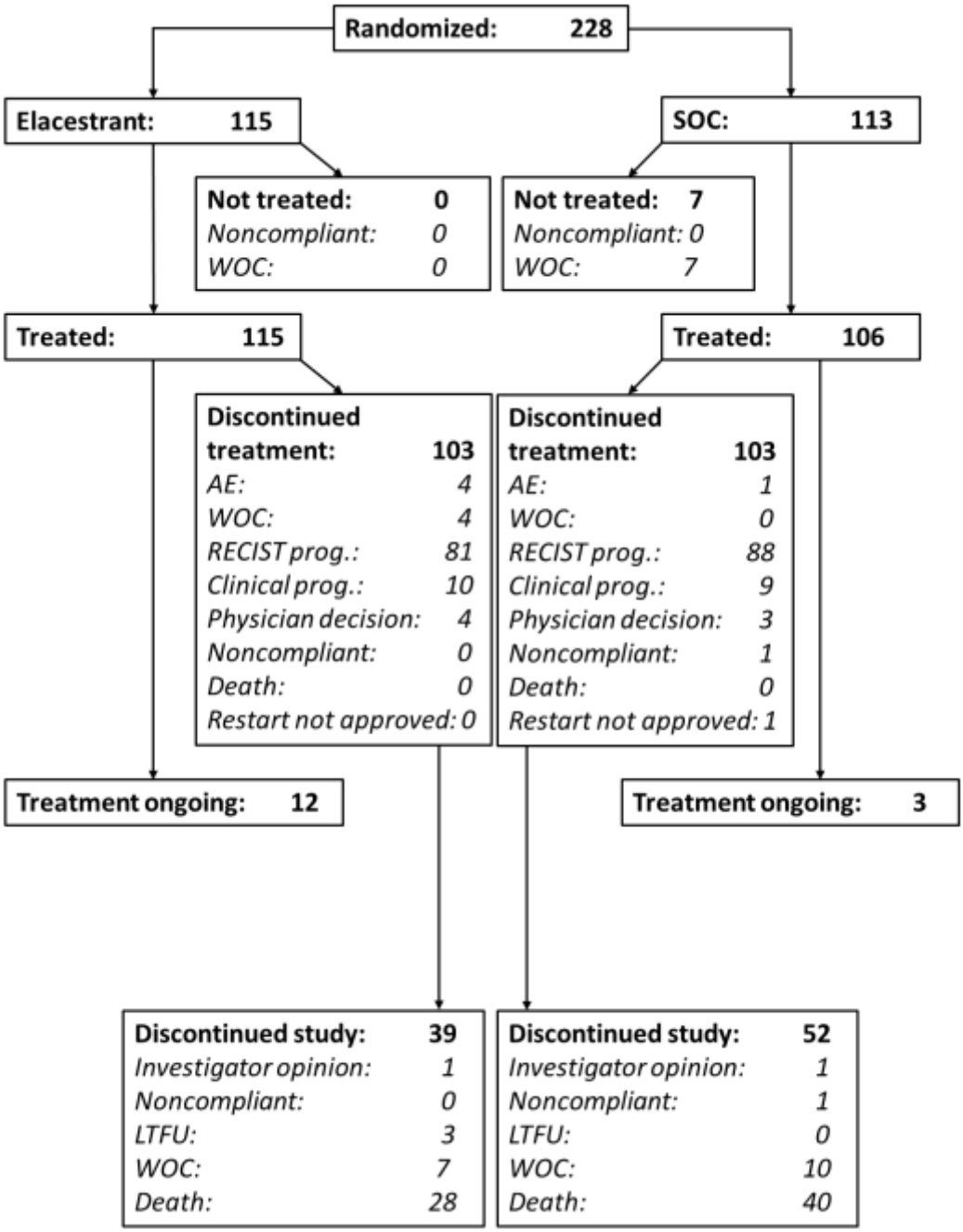
Of the randomised patients, 228 had an *ESR1-mut*, with 115 randomised to elacestrant and 113 to SOC.[33] Full details can be seen in Figure 8.

Seven patients (6.2%) withdrew from the study before being treated, all in the SOC group. At the clinical cut-off date for the analysis of all but the OS endpoint (DCO 6th September 2021), 12 patients in the elacestrant group (10.4%) and 3 patients in the SOC group (2.7%) were still on treatment. Reasons for treatment discontinuation mainly included investigator-assessed progression per RECIST criteria (81 [70.4%] in the elacestrant group vs. 88 [77.9%] in the SOC group) with much smaller numbers due to AEs, withdrawal of consent, clinical progression, physician decision, noncompliance and restart not approved. There were no deaths on treatment for patients with *ESR1-mut* in either treatment group.[98]

At the time of the PFS analysis, approximately half of patients with *ESR1-mut* who discontinued treatment remained in the study but were not receiving treatment. Thirty-nine (33.9%) patients in the elacestrant group and 52 (46%) patients in the SOC group had discontinued the study. The most common reason for discontinuing study participation was death (28 [24.3%] in the elacestrant group vs. 40 [35.4%] in the SOC group), but reasons also included investigator decision, noncompliance, withdrawal of consent and loss to follow up.[98]

At the time of the final OS analysis, in patients with *ESR1-mut*, 121 (53%) events had occurred (61 [53%] in the elacestrant group vs. 60 [53.1%] in the SOC group).[102]

Figure 8: EMERALD | Patient disposition for patients with *ESR1-mut* | DCO 6th September 2021



Abbreviations: AE, adverse event, *ESR1*, oestrogen receptor 1 gene; LTFU, lost to follow-up; prog, progression; RECIST, Response Evaluation Criteria in Solid Tumours; SOC, standard of care; WOC, withdrawal of consent

Source: EMERALD CSR *Data on File* (2023)[98]

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Quality assessment of EMERALD was conducted using the NICE checklist in the single technology appraisal and highly specialised technologies evaluation: User guide for company evidence submission template. This is adapted from the Systematic reviews: Centre for Reviews and Dissemination's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).[113] The full quality assessment for EMERALD can be found in Appendix D.

Assessment of the risk of biases concluded that EMERALD had a high risk of bias overall due to the open-label design. This is despite an appropriate randomisation scheme, well-balanced patient characteristics between the patient arms, no unexpected imbalances in dropouts between groups, and good quality assurance for the trial. Additionally, the population relevant indicated within the UK MA was a subgroup of the overall population, *ESR1-mut* (i.e. not the full ITT population). See Table 12 for full details.

B.2.5.1 Limitations of the evidence base

The strengths and limitations of EMERALD are presented in Section B.2.12.2, using data from the CSR and statistical analysis plan (SAP).[98,108] Limitations were not discussed in the EMERALD primary publication.[33]

Table 12: EMERALD | Quality assessment

Questions	EMERALD
Was randomisation carried out appropriately?	Yes. Investigators randomised eligible patients by Interactive Randomisation Technology. Random assignment was stratified according to *ESR1-mut* status, presence of visceral metastases, and previous treatment with fulvestrant.
Was the concealment of treatment allocation adequate?	No. EMERALD was an open-label study, thus, patients and investigators were not blinded to treatment assignment.
Were the groups similar at the outset of the trial in terms of prognostic factors?	Yes. Random assignment was stratified according to *ESR1-mut* status, presence of visceral metastases, and previous treatment with fulvestrant.
Were the care providers, patients and outcome assessors blind to treatment allocation?	No. EMERALD was an open-label study, thus, patients and investigators were not blinded to treatment assignment.
Were there any unexpected imbalances in dropouts between groups?	No.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes, but the population relevant to this submission was a subgroup of the overall population in line with the UK MA (i.e. not the full ITT population). Methods or accounting for missing data are detailed in the Statistical Analysis Plan.
Was there good quality assurance for this trial?	Yes, the trial was conducted in accordance with ICH GCP guidelines and regulatory requirements. Quality assurance audits were conducted.

Abbreviations: *ESR1*, oestrogen receptor 1 gene; ICH, International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; GCP, good clinical practice; ITT, intent-to-treat
Source, Bidard (2022)[33]

B.2.6 Clinical effectiveness results of the relevant trials

All data presented in this section are from the EMERALD trial; efficacy data are presented for patients with *ESR1-mut* (i.e. the population for the elacestrant marketing authorisation) and safety data are presented for All Patients and patients with *ESR1-mut*. Subgroup data for those patients with an *ESR1-mut* who received ≥12 months of prior ET + CDK4/6i (i.e. the proposed reimbursement population) are presented in Section B.2.7.2. Subgroup data for patients with *ESR1-mut* and *PIK3CA-mut* who received ≥12 months of prior ET + CDK4/6i (dual mutated) are presented in Section B.2.7.3.

For the *ESR1-mut* population, all efficacy results, excluding the final OS data (PFS, ORR, DOR, CBR), were analysed at the data cutoff of 6th September 2021. This was planned for after approximately 160 PFS events for patients with *ESR1-mut* had occurred.[33,98] However, the final PFS analysis was actually conducted after 140 events;[98] the decision to modify the plan was based on a blinded PFS event projection analysis prior to unblinding that showed an additional year would have been needed to observe the pre-specified number of events.[98] An interim OS analysis was carried out at the same time as the PFS analysis, but the final OS analysis occurred at the pre-specified number of events (121 [53.1%] in patients with *ESR1-mut*), as per the protocol (DCO 2nd September 2022).[102] Both analyses are presented.

For the two *post hoc* analyses, DCO were 2nd September 2022 for PFS and OS, and 8th July 2022 for patient-reported outcome (PRO) data.[100,101]

Median follow-up for efficacy analysis and safety analysis (excluding final OS analysis) was approximately 13.96 months.[98] Median follow-up for the final OS analysis was approximately 26.84 months.[102]

B.2.6.1 PFS | Primary efficacy endpoint | DCO 6th September 2021

Blinded IRC-assessed PFS for patients with *ESR1-mut* | Primary endpoint

PFS assessed by blinded IRC was statistically significantly prolonged in the elacestrant arm versus the SOC arm in patients with *ESR1-mut*, with an HR of 0.55 (95% CI: 0.39 to 0.77; Figure 9) and a stratified log-rank test p-value=0.0005.[33] Therefore, elacestrant was superior to SOC in patients with 1 or 2 lines of prior ET including a CDK4/6i (Table 13). Median PFS values were 3.8 months (95% CI: 2.17 to 7.26) versus 1.9 months (95% CI: 1.87 to 2.14) for the elacestrant versus SOC arm, respectively, in patients with *ESR1-mut*.[33,98,99]

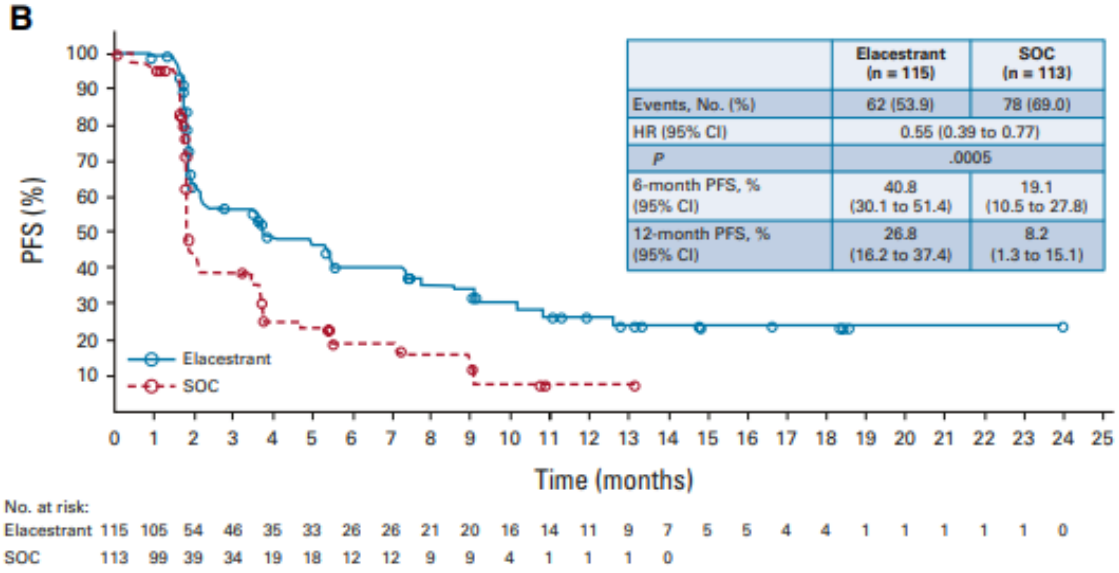
Of note, the Kaplan-Meier plot of PFS revealed an initial drop in both treatment arms; there are two potential reasons for this observation. Firstly, this is likely to indicate possible primary endocrine resistance. Secondly, this may be due to the timing of the assessments i.e. the first assessment occurred at 8 weeks and there were a low number of early response assessments over the initial period of observation. Since median PFS alone may not sufficiently interpret results in such a scenario, landmark PFS analyses were conducted at 3, 6, 12, and 18 months and favoured elacestrant at each timepoint (Table 13). In the patients with *ESR1-mut*, the 6- and 12-month PFS rates were 40.8% and 26.8%, respectively, in the elacestrant arm vs. 19.1% and 8.2% in the SOC arm.[33,98]

Given the influence of length of time on prior ET + CDK4/6i on subsequent treatment choice in ESMO guidelines,[12,77] this is an important consideration when considering data in this

setting. EMERALD is the only trial of an oral SERD that mandated prior CDK4/6i use for all patients and allowed enrolment of patients with primary endocrine resistance.[33] The study therefore provided the opportunity to analyse prior ET+ CDK4/6i duration as a potential surrogate marker for endocrine sensitivity and elacestrant efficacy. PFS was assessed by the length of time on prior CDK4/6i therapy before receiving elacestrant.

The results of the sensitivity analysis were consistent with the results of the primary analysis, as was the analysis in the per-protocol population.[98]

Figure 9: EMERALD | Kaplan–Meier plot for blinded IRC assessment of PFS | All patients with *ESR-1*-mut | Elacestrant vs. SOC | DCO 6th September 2021



	Elacestrant (n = 115)	SOC (n = 113)
Events, No. (%)	62 (53.9)	78 (69.0)
HR (95% CI)	0.55 (0.39 to 0.77)	
P	.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	19.1 (10.5 to 27.8)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.2 (1.3 to 15.1)

Footnotes: Median PFS and PFS rates 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. Hazard ratio and 95% CI were based on a stratified Cox's proportional hazard model with ties=Efron and the stratification factors prior treatment with fulvestrant and presence of visceral metastases; CI were calculated using a profile likelihood approach. P-value was generated by using a two-sided stratified log-rank test.
Abbreviations: CI, confidence interval; DCO, data cutoff; *ESR1*, oestrogen receptor 1 gene; HR, hazard ratio; IRC, imaging review committee; PFS, progression-free survival; SOC, standard of care
Source: Bidard (2022)[33]

Table 13: Blinded IRC-assessed PFS | All patients with *ESR1-mut* | DCO 6th September 2021

	Elacestrant N=115	SOC N=113
HR (95% CI) **p**	0.55 (0.39 to 0.77) 0.0005	
Median PFS months (95% CI)	3.8 (2.17 to 7.26)	1.9 (1.87 to 2.14)
Events, n (%) **Death** **Progression**	62 (53.9) 3 (2.6) 59 (51.3)	78 (69.0) 1 (0.9) 77 (68.1)

3-month PFS rate (95% CI)	55.93 (45.80 to 66.05)	39.55 (29.44 to 49.65)
6-month PFS rate (95% CI)	40.8% (30.1 to 51.4)	19.1% (10.5 to 27.8)
12-month PFS rate (95% CI)	26.8% (16.2 to 37.4)	8.2% (1.3 to 15.1
18-month PFS rate (95% CI)	24.33 (13.68 to 34.98)	-

Footnote: Median PFS and PFS rates 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. Hazard ratio and 95% CI were based on a stratified Cox's proportional hazard model with ties=Efron and the stratification factors prior treatment with fulvestrant and presence of visceral metastases; CI were calculated using a profile likelihood approach. P-value was generated by using a two-sided stratified log-rank test.
Abbreviations: CI, confidence interval; DCO, data cutoff; *ESR1*, oestrogen receptor 1 gene; HR, hazard ratio; IRC, imaging review committee; n, number of patients with the observed characteristic; N, total number in group; PFS, progression-free survival; SOC, standard of care
Source: Bidard 2023,[33] Bidard supplement 2023,[99] EMERALD CSR *Data on File* (2023)[98]

B.2.6.2 OS for patients with *ESR1-mut* | Key secondary endpoint

Overall survival | Interim analysis | DCO 6th September 2021

At the interim analysis of OS, 68 events had occurred in the *ESR1-mut* subgroup (28 in the elacestrant group and 40 in the SOC group), with an HR for death for the elacestrant treatment group versus the SOC treatment group of 0.59 (95% CI 0.36 to 0.96).[33] This gave a stratified log-rank test p-value of 0.0325.[33] Whilst this was not statistically significant, results did favour elacestrant (Table 14).[33,98]

The numbers of patients with any individual reason for censoring were generally similar across treatment groups with 87 patients (75.7%) in the elacestrant group vs. 73 patients (64.6%) in the SOC group (72 [62.6%] vs. 60 [53.1], respectively, were still in survival follow-up and were censored as such).[98]

Landmark analyses were conducted at 3, 6, 12, 18 and 24 months (Table 14) and the estimates at each of the timepoints consistently favoured the elacestrant arm.[33,98] The 6- and 12-month OS rates were 92.8% and 82.6%, respectively, in the elacestrant arm vs. 84.4% and 73.6% in the SOC arm.[33]

Table 14: OS interim analysis | All patients with *ESR1-mut* | DCO 6th September 2021

	Elacestrant N=115	**SOC N=113**
HR (95% CI) **p**	0.59 (0.36 to 0.96) 0.0325	
Median OS months (95% CI)	NC (18.60 – NC)	16.95 (14.00 – NC)
Events (death), n (%)	28 (24.3)	40 (35.4)
3-month OS rate (95% CI)	98.24 (95.82 to 100.0)	98.09 (95.46 to 100.0)
6-month OS rate (95% CI)	92.8 (88.0 to 97.6)	84.4 (77.3 to 91.4)
12-month OS rate (95% CI)	82.6 (75.3 to 90.0)	73.6 (64.8 to 82.4)
18-month OS rate (95% CI)	67.81 (56.22 to 79.40)	49.36 (37.03 to 61.70)
24-month OS rate (95% CI)	56.96 (39.85 to 74.07)	49.36 (37.03 to 61.70)

Footnotes: Median OS and OS rates calculated using Kaplan–Meier technique. CI for 25th, 50th (median) and 75th percentiles of OS are derived based on the Brookmeyer-Crowley method using a linear transformation. Hazard ratio and 95% CI were based on a stratified Cox's proportional hazard model with ties=Efron and the

stratification factors prior treatment with fulvestrant and presence of visceral metastases; CI were calculated using a profile likelihood approach. P value was generated by using a two-sided stratified log-rank test.
Abbreviations: CI, confidence interval; DCO, data cutoff; *ESR1*, oestrogen receptor 1 gene; HR, hazard ratio; n, number of patients with the observed characteristic; N, total number in group; NC, not calculated; OS, overall survival; SOC, standard of care
Source: Bidard 2023,[33] EMERALD CSR *Data on File* (2023)[98]

Overall survival | Final analysis | DCO 2nd September 2022

For OS, the final analysis occurred at the pre-specified number of events of 245 (51.3%) in the full population, as per the protocol.[102] This equated to 121 (53.1%) events in the *ESR1-mut* subgroup (61 [53%] in the elacestrant group and 60 [53.1%] in the SOC group). The HR for death for patients with *ESR1-mut* in the elacestrant treatment group versus the SOC treatment group was 0.903 (95% CI 0.629 to 1.298). This gave a stratified log-rank test p-value of 0.5823. Whilst this was not statistically significant, results did favour elacestrant (Table 15).[102]

The numbers of patients with any individual reason for censoring were generally similar across treatment groups in patients with *ESR1-mut*; 54 patients (47%) in the elacestrant group vs. 53 patients (46.9%) in the SOC group (38 [33%] vs. 39 [34.5%], respectively, were still in survival follow-up and censored as such).[102]

Landmark analyses were conducted at 3, 6, 12, 18 and 24 months (Table 15) and the estimates at each of the timepoints consistently favoured the elacestrant arm. The 6- and 12-month OS rates were 92.79 % and 83.11%, respectively, in the elacestrant arm vs. 84.36% and 74.38% in the SOC arm.[102]

Table 15: OS final analysis | All patients with *ESR1-mut* | DCO 2nd September 2022

	Elacestrant N=115	SOC N=113
HR (95% CI) **p**	0.903 (0.629 to 1.298) 0.5823	
Median OS months (95% CI)	24.18 (20.53 – 28.71)	23.49 (15.64 – 29.90)
Events (death), n (%)	61 (53)	60 (53.1)
3-month OS rate (95% CI)	98.24 (95.82 to 100.0)	98.09 (95.46 to 100.0)
6-month OS rate (95% CI)	92.79 (87.97 to 97.60)	84.36 (77.32 to 91.40)
12-month OS rate (95% CI)	83.11 (75.98 to 90.25)	74.38 (65.88 to 82.89)
18-month OS rate (95% CI)	69.09 (60.15 to 78.04)	53.27 (43.50 to 63.04)
24-month OS rate (95% CI)	50.71 (40.91 to 60.52)	49.02 (39.18 to 58.87)

Footnotes: Median OS and OS rates calculated using Kaplan–Meier technique. CI for 25th, 50th (median) and 75th percentiles of OS are derived based on the Brookmeyer-Crowley method using a linear transformation. Hazard ratio and 95% CI were based on a stratified Cox's proportional hazard model with ties=Efron and the stratification factors prior treatment with fulvestrant and presence of visceral metastases; CI were calculated using a profile likelihood approach. P-value was generated by using a two-sided stratified log-rank test.
Abbreviations: CI, confidence interval; DCO, data cutoff; *ESR1*, oestrogen receptor 1 gene; HR, hazard ratio; n, number of patients with the observed characteristic; N, total number in group; OS, overall survival; SOC, standard of care
Source: EMERALD OS Addendum to CSR *Data on File* (2023)[102]

B.2.6.3 Response for patients with *ESR1-mut* | Secondary endpoint | DCO 6th September 2021

Blinded IRC-assessed ORR for patients with *ESR1-mut* | Secondary endpoint

The ORR (based on confirmed PR as assessed by the blinded IRC for the RE population) for patients with *ESR1-mut* was slightly higher in the elacestrant group (6 patients [7.1%]) than in the SOC group (4 patients [4.7%]), but the difference in ORR was not statistically significant with a p-value of 0.499 (Table 16). No patients had a CR.[98,99]

Blinded IRC-assessed DOR for patients with *ESR1-mut* | Secondary endpoint

DOR for blinded IRC assessment is shown in Table 16. All patients with *ESR1-mut* with a response in the elacestrant group were censored without progression or death by the cutoff date, so no DOR could be calculated. For the 4 responders in the SOC arm, the median DOR was 5.55 months and the longest DOR was 5.6 months.[98,99]

Table 16: Blinded IRC-assessed ORR and DOR | RE patients with *ESR1-mut* | DCO 6th September 2021

	Elacestrant N=85	SOC N=86
Best OR, n (%)		
CR (confirmed)	0	0
PR (confirmed)	6 (7.1)	4 (4.7)
SD ≥6 weeks	42 (49.4)	22 (25.6)
PD	32 (37.6)	55 (64)
NE	5 (5.9)	5 (5.8)
ORR[a], n (%) [95% CI] **p**	6 (7.1) [2.6 to 14.7] 0.499	4 (4.7) [1.3 to 11.5] 0.499
Median DOR[b], months (95% CI) [range]	NC (NC to NC) [1.9+ to 14.6+]	5.55 (3.71 to NC) [3.7 to 5.6+]
Censored patients with CR or PR[C], n (%)	6 (100)	2 (50)

Footnotes: [a]p value used the stratified Cochrane–Mantel–Haenszel test with stratification factors of prior treatment with fulvestrant and presence of visceral metastases (or stratified logistic regression if the Mantel–Fliess criterion is not met for the validity of the Cochrane–Mantel–Haenszel test). Binomial Clopper–Pearson 95% confidence interval. [b]Calculated using the Kaplan–Meier method. CI are constructed based on the Brookmeyer–Crowley method using linear transformation. [C]Percentage is calculated using number of patients with confirmed CR or PR as the denominator.
Abbreviations: CI, confidence interval; CR, complete response; DCO, data cutoff; DOR, duration of response; *ESR1*, oestrogen receptor 1 gene; IRC, imaging review committee; n, number of patients with the observed characteristic; N, total number in group; NE, not evaluable; OR, overall response; ORR, objective response rate; PD, progressive disease; PR, partial response; RE, response evaluable; SD, stable disease; SOC, standard of care
Source: Bidard supplement 2023,[99] EMERALD CSR *Data on File* (2023)[98]

Blinded IRC-assessed CBR at 24 weeks for patients with *ESR1-mut* | Secondary endpoint

There were no patients with a CR, so the CBR consists of patients with any best OR of PR or SD sustained for at least 24 weeks (see Table 17).[98]

Among patients with *ESR1-mut*, the IRC-assessed CBR was 26 (24.1%) in the elacestrant group and 12 (11.5%) in the SOC group, p=0.024.[99] For full results see Table 17.[98,99]

Table 17: Blinded IRC-assessed CBR | CBE patients with *ESR1-mut* | DCO 6th September 2021

	Elacestrant N=108	SOC N=104
Best OR, n (%)		
CR (confirmed)	0 (0)	0 (0)
PR (confirmed)	6 (5.6)	4 (3.8)
SD ≥24 weeks	20 (18.5)	8 (7.7)
PD	53 (49.1)	72 (69.2)
NE*	29 (26.9)	20 (19.2)
CBR, n (%) [95% CI] **p**	26 (24.1) [16.4 to 33.3] 0.024[a]	12 (11.5), [6.1 to 19.3] 0.024[a]

Footnotes: *NE includes patients with SD between 6 weeks and 24 weeks. [a]P-value used a stratified Cochran-Mantel-Haenszel test, with the stratification factors of prior treatment with fulvestrant and presence of visceral metastases. Binomial Clopper-Pearson 95% CI.
Abbreviations: CI, confidence interval; CBE, clinical benefit evaluable**;** CBR, clinical benefit rate; CR, complete response; DCO, data cutoff; *ESR1*, oestrogen receptor 1 gene; IRC, imaging review committee; n, number of patients with the observed characteristic; N, total number in group; NE, not evaluable; OR, overall response; PD, progressive disease; PR, partial response; RE, response evaluable; SD, stable disease; SOC, standard of care
Source: Bidard supplement 2023,[99] EMERALD CSR *Data on File* (2023)[98]

B.2.6.4 Patient-reported outcomes for the patients with *ESR1-mut* | DCO 6th September 2021

Patient-reported outcomes (PROs) were evaluated using the PRO tools: the EuroQol 5 Dimension 5 Level (EQ-5D-5L), the EORTC-QLQ-C30 and the Patient-Reported Outcome Common Terminology Criteria for Adverse Events (PRO-CTCAE) questionnaires. These were completed periodically throughout the treatment period (C1D1, C1D15 [± 2 days], C2D1, D1 of subsequent cycles [± 2 days] up to C4 then D1 of every other cycle starting with C6), at the EOT (+ 14 days) and at the post-treatment safety follow-up visit 30 days after the last dose of study drug (± 3 days).[98]

Overall, QoL was maintained between treatment groups in the EMERALD trial and over time, and results were similar to those for All Patients. 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. PRO-CTCAE results showed no clinically meaningful differences between treatment groups, and no noteworthy changes over time for change in patient-reported frequency, severity, or interference of symptoms from any TEAE.

EQ-5D-5L scores were comparable across treatment arms with no notable differences over time and no meaningful change from baseline.[114]

EQ-5D-5L and EQ-VAS

The EQ-5D-5L included data from both the EQ-5D descriptive system and the visual analogue scale (VAS).

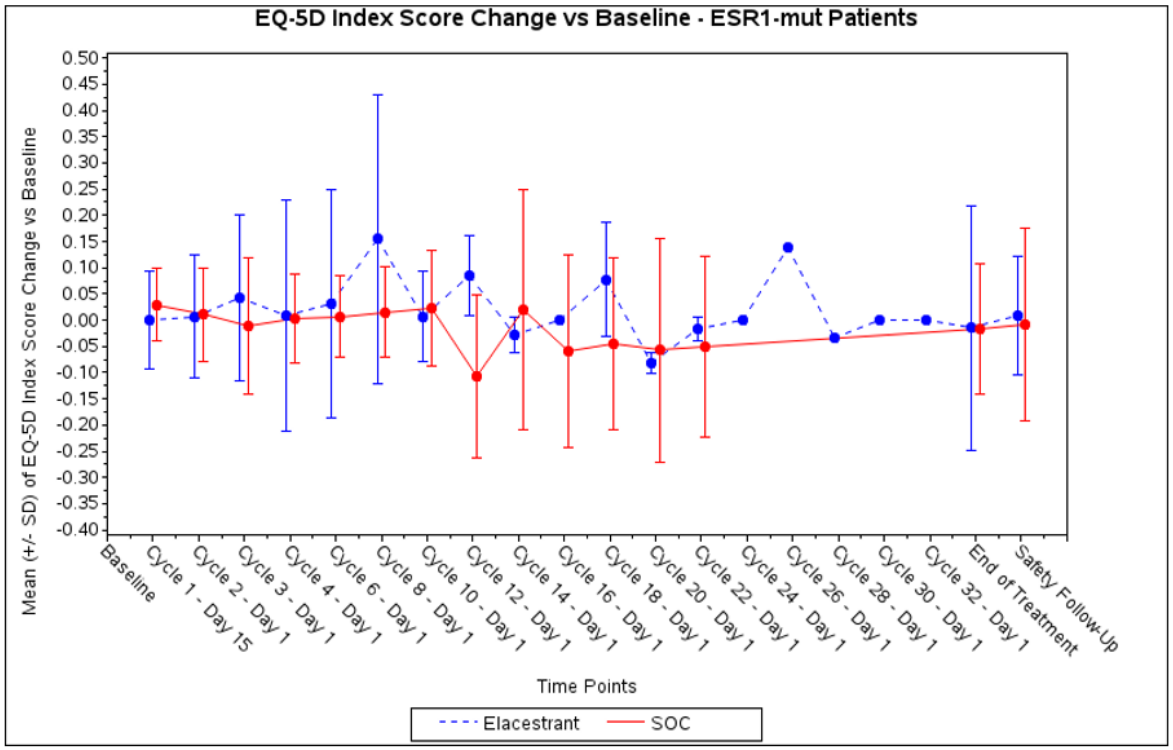
Among patients with *ESR1-mut*, the mean EQ-5D-5L index scores at EOT were similar for elacestrant 0.73 (0.245) and SOC 0.81 (0.200), with no notable differences over time. Similarly, there was no meaningful mean (SD) change from baseline in either the elacestrant group -0.01 (0.243) or the SOC group -0.01 (0.119), see Table 18 for results. Similarly, for the EQ-VAS there were no noteworthy differences between groups in change from baseline to EOT (see Figure 10) and no noteworthy changes over time in either group.

Table 18: EQ-5D-5L Index score and EQ-VAS score | All patients with *ESR1-mut* | DCO 6th September 2021

	Elacestrant N=115	SOC N=113
EQ-5D-5L Index score		
Baseline	N=50	N=50
Mean (SD)	0.76 (0.208)	0.83 (0.123)
End of treatment	N=34	N=38
Mean (SD)	0.73 (0.245)	0.81 (0.200)
Change from baseline	N=32	N=37
Mean (SD)	-0.01 (0.243)	-0.01 (0.119)
EQ-VAS score		
Baseline	N=108	N=98
Mean (SD)	73.7 (18.15)	73.4 (16.76)
End of treatment	N=74	N=78
Mean (SD)	67.2 (22.17)	69.4 (22.24)
Change from baseline	N=72	N=75
Mean (SD)	-8.7 (18.65)	-2.8 (16.95)

Abbreviations: DCO, data cutoff; EQ-5D-5L, EuroQoL Five-dimension Five-level; EQ-VAS, EuroQoL visual analogue scale; *ESR1*, oestrogen receptor 1 gene; SD, standard deviation; SOC, standard of care
Source: EMERALD CSR *Data on File* (2023)[98], EMERALD: UK Requests additional PRO *Data on File*[115]

Figure 10: Mean (+/-SD) of EQ-5D Index Score Change from Baseline by visit | All patients with patients with ESR-1 | Elacestrant vs. SOC | DCO 8th of July



Abbreviations: DCO, data cutoff; EQ-5D-5L, EuroQoL Five-dimension Five-level; EQ-VAS, EuroQoL visual analogue scale; *ESR1*, oestrogen receptor 1 gene; SD, standard deviation; SOC, standard of care
Source: EMERALD: UK Requests additional PRO *Data on File*[115]

EORTC QLQ-C30

Table 19No noteworthy differences were observed between treatment groups and there were no noteworthy changes over time in either group regarding the MMRM analysis of HRQoL through cycle 6.

Table 19: Change from baseline to EOT in EORTC QLQ-C30 functional scales, quality of life, and symptom scales | All patients with *ESR1-mut* | DCO 6th September 2021

	Elacestrant N=115	SOC N=113
Functional scales		
Physical functioning	N=72	N=72
Mean (SD)	-7.685 (22.9215)	-1.759 (15.6244)
Role functioning	N=72	N=73
Mean (SD)	-10.417 (29.1289)	-0.457 (27.2127)
Emotional functioning	N=72	N=72
Mean (SD)	-4.321 (20.3265)	-1.736 (21.6647)

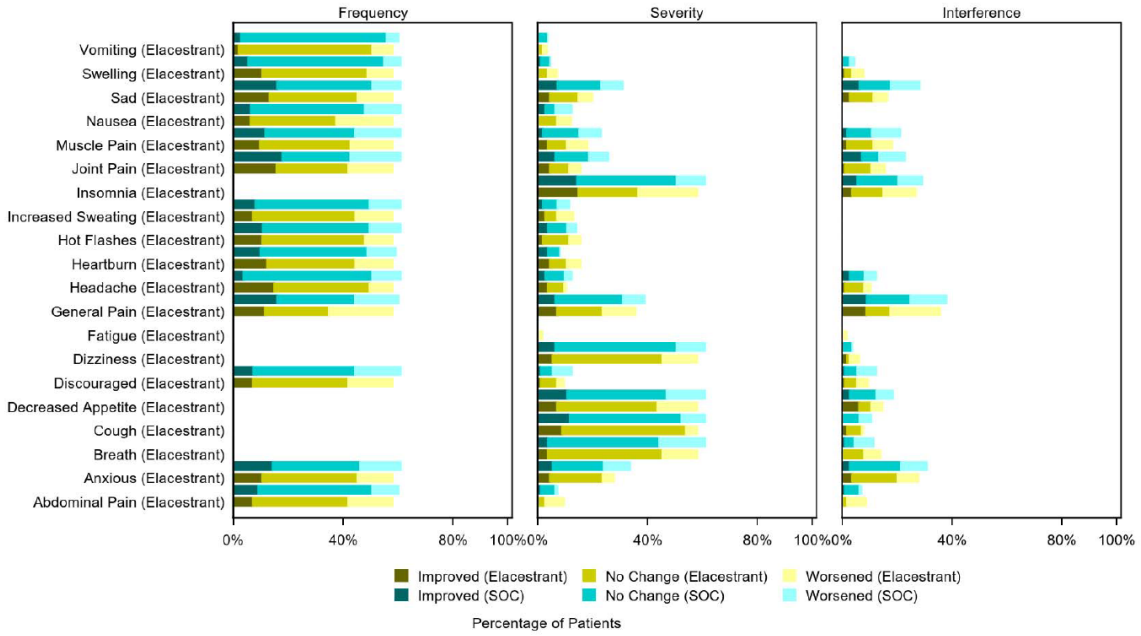
Cognitive functioning	N=72	N=72
Mean (SD)	-5.093 (21.7826)	-3.009 (17.7635)
Social functioning	N=72	N=73
Mean (SD)	-6.944 (28.3547)	-4.110 (24.8111)
Quality of life	N=72	N=73
Mean (SD)	-9.954 (22.0097)	-4.110 (23.4111)
Symptoms scales		
Fatigue	N=72	N=72
Mean (SD)	9.722 (24.3102)	0.772 (17.9187)
Nausea and vomiting	N=72	N=72
Mean (SD)	7.870 (22.1978)	5.787 (21.1485)
Pain	N=72	N=72
Mean (SD)	9.491 (28.0881)	1.620 (22.2308)
Dyspnoea	N=72	N=72
Mean (SD)	3.241 (15.9809)	8.796 (27.4036)
Insomnia	N=72	N=73
Mean (SD)	2.315 (28.1547)	3.196 (27.3096)
Appetite loss	N=72	N=72
Mean (SD)	10.185 (24.1532)	0.000 (19.3801)
Constipation	N=72	N=73
Mean (SD)	-2.315 (24.5946)	2.740 (23.4082)
Diarrhoea	N=72	N=72
Mean (SD)	3.704 (19.0178)	0.926 (17.6669)
Financial difficulties	N=72	N=71
Mean (SD)	-0.926 (16.7577)	-1.408 (17.3082)

Abbreviations: DCO, data cutoff; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EOT, end of treatment; *ESR1*, oestrogen receptor 1 gene; SD, standard deviation; SOC, standard of care
Source: EMERALD CSR *Data on File* (2023)[98]

PRO-CTCAE

There were no noteworthy differences between treatment groups and no noteworthy changes over time in either the elacestrant or SOC group for change from baseline in frequency, severity, or interference for any TEAE (see Figure 11).

Figure 11: PRO-CTCAE, stacked bar chart for change from baseline to EOT in percentage of categories of PRO-CTCAE | All patients with *ESR1-mut* | Elacestrant vs. SOC | DCO 6th September 2021



Abbreviations: DCO, data cutoff; EOT, end of treatment; *ESR1*, oestrogen receptor 1 gene; PRO-CTCAE, Patient-Reported Outcome Common Terminology Criteria for Adverse Events; SOC, standard of care
Source: EMERALD CSR *Data on File* (2023)[98]

B.2.6.5 Time to chemotherapy

Patients who received another therapy (other than chemotherapy) as their first post-study therapy were not considered in this analysis.

In the patients who received chemotherapy as first systemic therapy after treatment discontinuation (50 patients in the elacestrant group and 59 patients in the SOC group), the mean (SD) time from randomisation to chemotherapy was 105.8 (63.04) days in the elacestrant group and 102.8 (71.31) days in the SOC group.[98]

B.2.6.6 Efficacy conclusions

The EMERALD trial compared elacestrant (a next-generation, nonsteroidal, orally bioavailable SERD that binds to ERα and causes its degradation in a dose-dependent manner through the proteasomal pathway), to SOC. Patient baseline characteristics for patients with *ESR1-mut* in EMERALD are presented in Table 9, and were generally well balanced between treatment arms.[33,98]

The primary objective of superior PFS for elacestrant relative to SOC treatment in patients with *ESR1-mut* was met. PFS assessed by blinded IRC was statistically significantly prolonged in the elacestrant arm versus the SOC arm in patients with *ESR1-mut*, with an HR of 0.55 (95% CI: 0.39 to 0.77) and a stratified log-rank test p-value=0.0005.[33,98] Therefore, elacestrant was superior to SOC in patients with 1 or 2 lines of prior ET including a

CDK4/6i.[33,98] Landmark PFS analyses were conducted at 3, 6, 12, and 18 months and favoured elacestrant at each timepoint: 55.93% vs. 39.55% at 3 months, 40.8% vs. 19.1% at 6 months, 26.8% vs. 8.2% at 12 months and 24.33% vs. NC (not calculable) at 18 months for elacestrant vs. SOC.[33,98]

The findings of the PFS per IRC were reinforced by the analysis of secondary endpoints, including the key secondary endpoint OS and sensitivity analysis, which numerically favoured the elacestrant arm.[98,99] Whilst OS results were not significant, they favoured elacestrant at the interim analysis of OS (HR 0.59; 95% CI: 0.36 to 0.96, p=0.0325)[33,98] and the final analysis of OS (HR 0.903; 95% CI: 0.629 to 1.298, p=0.5823),[102] as did estimates of OS at various timepoints, consistent with the PFS landmark analyses. Additionally, HRs for PFS numerically favoured elacestrant across pre-specified subgroups, with all below 1 for the *ESR1-mut* population (see Section B.2.7 and Appendix E for further details).

QoL was maintained between treatment groups in the EMERALD trial and over time, and results were similar to those for All Patients. EORTC QLQ-C30 scores were generally similar across treatment groups and time. PRO-CTCAE results showed no clinically meaningful differences between treatment groups, and no noteworthy changes over time for change in patient-reported frequency, severity, or interference of symptoms from any TEAE. EQ-5D-5L scores were comparable across treatment arms with no notable differences over time and no meaningful change from baseline.[114]

Overall, results indicate that elacestrant shows a clinically meaningful and significant 45% reduction in the risk of progression or death vs. SOC. Elacestrant demonstrates superiority in PFS over SOC endocrine monotherapy in patients with *ESR1-mut*, ER+/HER2-, locally advanced or mBC post CDK4/6i.[33]

B.2.7 Subgroup analysis

Pre-specified subgroup analyses were performed for IRC-assessed PFS, OS, ORR, DOR and CBR in the same manner as the analyses for all patients with *ESR1-mut*, unless the number of patients in the subgroup in each treatment group was not sufficiently large (e.g. <5%). Please see Appendix E for further information.

Several additional *post hoc* subgroup analyses were performed following DCO 6th September 2021. Subgroup data for those patients with an *ESR1-mut* who received ≥12 months of prior ET + CDK4/6i (i.e. the proposed reimbursement population) and subgroup data for patients with *ESR1-mut, PIK3CA-mut* who received ≥12 months of prior ET + CDK4/6i (dual mutated) are reported here. These have been included as the populations that will be considered in the economic evaluation given the stated comparators.

Results of *post hoc* subgroup analyses were not powered to detect statistical significance.

B.2.7.1 *Post hoc* subgroup analyses baseline characteristics

Patient baseline demographic and disease characteristics for all patients with *ESR1-mut* and dual mutated patients (*ESR1-mut* and *PIK3CA-mut*), who had received ≥12 months of prior ET + CDK4/6i are presented in Table 20. Groups were well balanced with respect to all baseline disease and demographic characteristics and results were similar to the *ESR1-mut* population as a whole.

Table 20: EMERALD | Baseline characteristics for *post hoc* subgroup analysis | All patients with *ESR1-mut and* ≥12 months of prior ET + CDK4/6i and patients with *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i (dual mutated)

	All patients with *ESR1-mut* who had received ≥12 months of prior ET + CDK4/6i		Patients with *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i (dual mutated)	
Characteristic	**Elacestrant N=78**	**SOC N=81**	**Elacestrant N=27**	**SOC N=35**
Median age, years (range)	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
Female, n (%)	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])
Race (patients could select >1) or ethnicity, n (%)				
White	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])
Asian	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])
Black or African American	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])
Other	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])
Hispanic	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])

Unknown	[redacted]	[redacted]	[redacted]	[redacted]
ECOG performance status, n (%)				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
>1	[redacted]	[redacted]	[redacted]	[redacted]
Visceral metastasis[a], n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Prior adjuvant therapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Prior therapies for advanced or metastatic disease, n (%)				
Prior CDK4/6i	78 (100.0)	81 (100.0)	27 (100.0)	35 (100.0)
Any prior ET[b]	[redacted]	[redacted]	[redacted]	[redacted]
Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]
AI	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]	[redacted]	[redacted]
mTOR inhibitor	[redacted]	[redacted]	[redacted]	[redacted]
PI3K inhibitor	[redacted]	[redacted]	[redacted]	[redacted]
No. of prior lines of ET in the advanced or metastatic setting, n (%)				
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
No. of prior lines of chemotherapy in the advanced or metastatic setting, n (%)				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a]Includes lung, liver, brain, pleural, and peritoneal involvement; [b]Remaining patients progressed during or within 12 months of adjuvant endocrine therapy

Abbreviations: AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ECOG, Eastern Cooperative Oncology Group; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; mTOR, mammalian target of rapamycin; n, number; PI3K, phosphatidylinositol 3 kinase

Source: EMERALD 12 month+ *post hoc* analysis *Data on File* (2023)[100]; EMERALD dual mutation population 12 month+ *post hoc* analysis *Data on File (2023)*[101]

B.2.7.2 *Post hoc* subgroup analysis | Patients with *ESR1-mut* and ≥12 months of prior ET + CDK4/6i

For patients with ER+/HER2- advanced/mBC who do not require chemotherapy (which is mainly indicated when there is a risk of imminent organ failure), SOC treatment in the advanced/metastatic setting is ET + CDK4/6i.[12] While 20% of patients with ER+/HER2- advanced/mBC progress rapidly on ET + CDK4/6i and are unlikely to benefit from further ET, many patients acquire resistance to ET + CDK4/6i over a longer time period.[13] Given the influence of length of time on ET + CDK4/6i on subsequent treatment choice in ESMO guidelines,[12,77] this is an important consideration when considering data in this setting. EMERALD is the only trial of an oral SERD that mandated prior CDK4/6i use for all patients and allowed enrolment of patients with primary endocrine resistance.[33] The study therefore provided the opportunity to analyse prior ET+ CDK4/6i duration as a potential surrogate marker for endocrine sensitivity and elacestrant efficacy.

The purpose of this subgroup analysis was to understand the efficacy of elacestrant in the population within EMERALD who had long exposure to ET + CDK4/6i (i.e. ≥12 months).

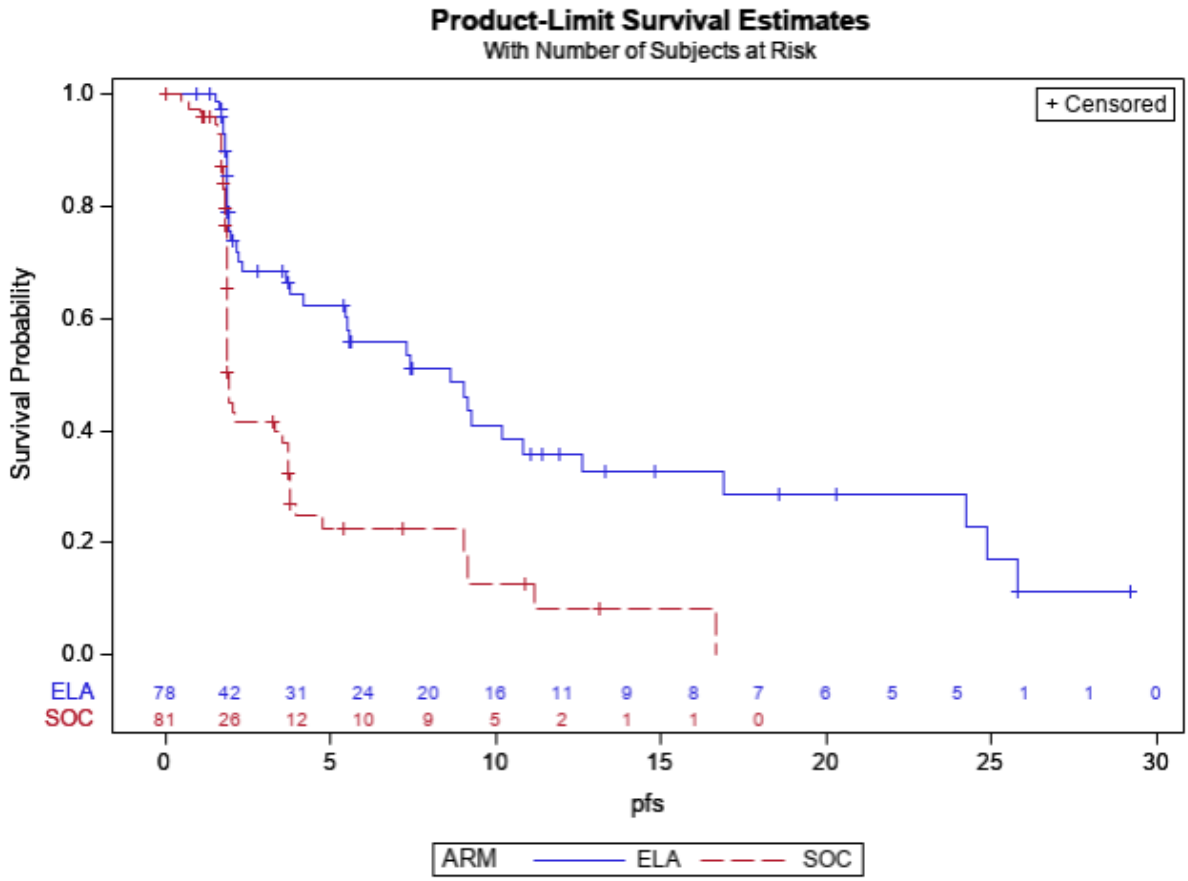
B.2.7.2.1 Blinded IRC-assessed PFS | DCO 2nd September 2022

A *post hoc* subgroup analysis showed that the duration of prior ET + CDK4/6i in the metastatic setting was positively associated with PFS (the longer the duration of prior ET + CDK4/6i, the longer PFS on elacestrant vs. SOC). Of the 159 patients in this *post hoc* analysis, 78 were in the elacestrant arm and 81 in the SOC arm.[28,30,100]

An absolute increase of 6.7 months in median PFS was observed in patients with ≥12 months of prior ET + CDK4/6i therapy with elacestrant (8.61 months; 95% CI 4.14 to 10.84) vs. SOC (1.91 months; 95% CI: 1.87 to 3.68), with an HR of 0.410; 95% CI: 0.262 to 0.634, p <0.0001. Significance cannot be inferred as the study was not powered for this analysis.[28,30,100] A Kaplan–Meier plot of PFS is shown in Figure 12.

Landmark PFS analyses were conducted at 3, 6, 12, and 18 months and favoured elacestrant at each timepoint (all results can be seen in Table 21). The 6- and 12-month PFS rates were 55.81% and 35.81%, respectively, in the elacestrant arm vs. 22.66% and 8.39%, respectively, in the SOC arm.[30,100]

Figure 12: Kaplan–Meier plot of IRC-assessed PFS in patients with *ESR1-mut* who had received ≥12 months of prior ET + CDK4/6i | Elacestrant vs. SOC | DCO 2nd September 2022



Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DCO, data cutoff; ELA, elacestrant; *ESR1*, oestrogen receptor 1 gene; IRC, imaging review committee; PFS, progression-free survival; SOC, standard of care
Source: EMERALD 12 month+ *post hoc* analysis *Data on File* (2023)[100]

Table 21: Blinded IRC-assessed PFS | All patients with *ESR1-mut* who had received ≥12 months of prior ET + CDK4/6i | DCO 2nd September 2022

	Elacestrant N=78	SOC N=81
HR (95% CI) **p**	0.410 (0.262 to 0.634) <0.0001	
Median PFS months (95% CI)	8.61 (4.14 to 10.84)	1.91 (1.87 to 3.68)
Events, n (%) **Death** **Progression**	39 (50) 1 (1.3) 38 (48.7)	53 (65.4) 1 (1.2) 52 (64.2)
3-month PFS rate (95% CI)	68.30 (56.67 to 79.93)	41.55 (29.19 to 53.90)
6-month PFS rate (95% CI)	55.81 (42.69 to 68.94)	22.66 (11.63 to 33.69)
12-month PFS rate (95% CI)	35.81 (21.84 to 49.78)	8.39 (0.00 to 17.66)

18-month PFS rate (95% CI)	28.49 (14.08 to 42.89)	0.00 (-)

Footnotes: 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. 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), CI calculated using a profile likelihood approach. The p-value was generated by using a two-sided stratified log-rank test
Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; DCO, data cutoff; *ESR1*, oestrogen receptor 1 gene; HR, hazard ratio; IRC, imaging review committee; n, number of patients with the observed characteristic; N, total number in group; PFS, progression-free survival; SOC, standard of care
Source: Bardia (2023)[30], Bardia (2023)[28], EMERALD 12 month+ *post hoc* analysis *Data on File* (2023)[100]

B.2.7.2.2 Overall Survival | DCO 2nd September 2022

At the time of the *post hoc* OS analysis, [redacted] ([redacted]) death events had occurred in the elacestrant group vs. [redacted] ([redacted]) in the SOC group. The HR for death for patients with *ESR1-mut* in the elacestrant treatment group versus the SOC treatment group was [redacted] (95% CI: [redacted] to [redacted], [redacted]), see Table 22. There was [redacted] median OS [redacted] seen with elacestrant ([redacted] months; 95% CI [redacted] to [redacted]) vs. SOC ([redacted] months; 95% CI: [redacted] to [redacted]). A Kaplan–Meier plot is shown in Figure 13.[100]

The numbers of patients with any individual reason for censoring were [redacted] across treatment groups: [redacted] patients ([redacted]) in the elacestrant group vs. [redacted] patients ([redacted]) in the SOC group – [redacted] ([redacted]) vs. [redacted] ([redacted]) censored as still in survival follow-up and [redacted] ([redacted]) vs. [redacted] ([redacted]) censored due to withdrawn consent for elacestrant vs. SOC respectively.[100]

Landmark analyses were conducted at 3, 6, 12, 18 and 24 months (Table 22) and the [redacted]-month timepoint [redacted] the elacestrant arm.[100]

Figure 13: Kaplan–Meier plot for OS | All patients with *ESR1-mut* who had received ≥12 months of prior ET + CDK4/6i | Elacestrant vs. SOC | DCO 2nd September 2022

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DCO, data cutoff; *ESR1*, oestrogen receptor 1 gene; OS, overall survival; SOC, standard of care
Source: EMERALD 12 month+ *post hoc* analysis *Data on File* (2023)[100]

Table 22: OS | All patients with *ESR1-mut* who had received ≥12 months of prior ET + CDK4/6i | DCO 2nd September 2022

	Elacestrant N=78	SOC N=81
HR (95% CI)	[redacted] ([redacted] to [redacted])	
p	[redacted]	
Median OS months (95% CI)	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
Events (death), n (%)	[redacted] ([redacted])	[redacted] ([redacted])
3-month OS rate (95% CI)	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
6-month OS rate (95% CI)	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
12-month OS rate (95% CI)	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
18-month OS rate (95% CI)	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
24-month OS rate (95% CI)	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])

Footnotes: Calculated using Kaplan–Meier technique. CI for 25th, 50th (median) and 75th percentiles of OS are derived based on the Brookmeyer-Crowley method using a linear transformation. 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), CI calculated using a profile likelihood approach. The p-value was generated by using a two-sided stratified log-rank test
Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; DCO, data cutoff; *ESR1*, oestrogen receptor 1 gene; HR, hazard ratio; n, number of patients with the observed characteristic; N, total number in group; OS, overall survival; SOC, standard of care
Source: EMERALD 12 month+ *post hoc* analysis *Data on File* (2023)[100]

B.2.7.2.3 Patient-Reported Outcomes | DCO 8th July 2022

Overall, HRQoL data for the subgroup of patients with *ESR1-mut* who had received ≥12 months of prior ET + CDK4/6i were consistent with those reported for All Patients and all patients with *ESR1-mut* (see Section B.2.6.4).

The mean (SD) EQ-5D-5L index scores at EOT were similar for elacestrant [redacted] ([redacted]) and SOC [redacted] ([redacted]), with no notable differences over time. Similarly, there was no meaningful mean (SD) change from baseline in either elacestrant [redacted] ([redacted]) or SOC [redacted] ([redacted]).[100] Please see Appendix E for further details.

B.2.7.2.4 Adverse reactions | Treatment compliance, exposure and most common TEAEs

Overall, safety data for the subgroup of patients with *ESR1-mut* who had received ≥12 months of prior ET + CDK4/6i were consistent with those reported for All Patients and all patients with *ESR1-mut* (see Section B.2.10).

Most AEs were Grade 1 or 2, with very few Grade ≥3 events reported. At least one TEAE of any Grade was reported for [redacted] ([redacted]) patients in the elacestrant arm and [redacted] ([redacted]) in the SOC arm. The most common TEAEs reported for elacestrant were nausea (30 [38.5%]), arthralgia ([redacted] [redacted]), and diarrhoea and vomiting (both 16 [20.5%]). The most common TEAEs reported for SOC were arthralgia ([redacted] [redacted]) and nausea, elevated alanine aminotransferase, and elevated aspartate aminotransferase (all [redacted] [redacted%]).[100] Please see Appendix E for further detail.

B.2.7.3 *Post hoc* subgroup analysis | Dual mutated (*ESR1-mut* and *PIK3CA-mut)* and ≥12 months of prior ET + CDK4/6i)

There are no targeted treatments specifically indicated for *ESR1*-mutated BC and in the absence of this, based on UK clinical feedback, for patients with both a *PIK3CA-mut* and *ESR1-mut* (dual mutated), alpelisib in combination with fulvestrant (per TA816) is the relevant comparator.[20] B.2.1A *post hoc* analysis was conducted on EMERALD data to look at those patients who possessed mutations in both *ESR1* and *PIK3CA* (*ESR1-mut* + *PIK3CA-mut*).[28,101]

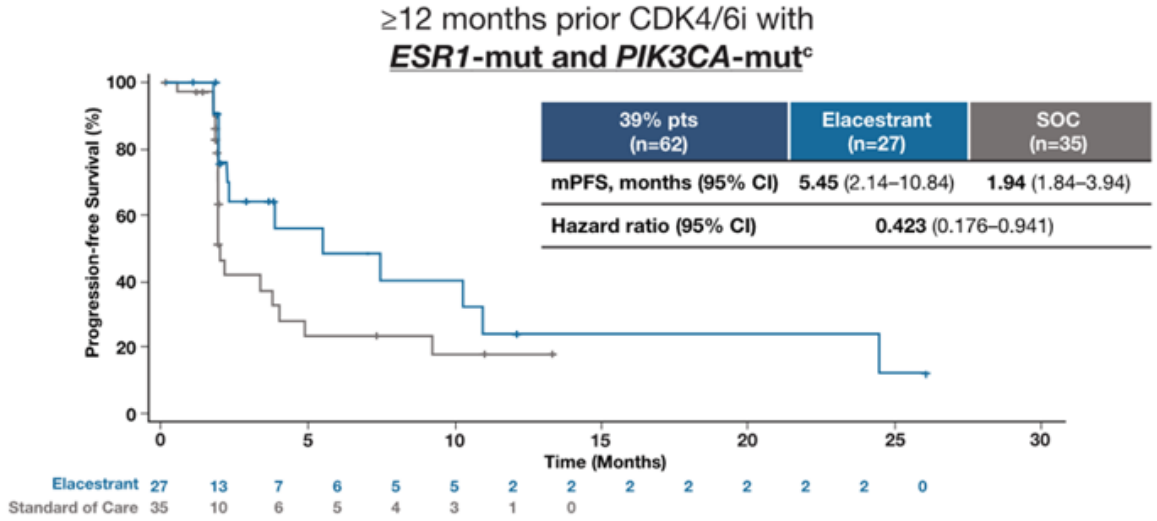
B.2.7.3.1 Blinded IRC-assessed PFS | DCO 2nd September 2022

PFS in patients with *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i (dual mutated), was longer in patients treated with elacestrant than those treated with SOC. Of the 62 patients in this *post hoc* analysis, 27 were in the elacestrant arm and 35 in the SOC arm.[28]

An absolute increase of 3.51 months in median PFS was observed with elacestrant (5.45 months; 95% CI 2.14 to 10.84) vs. SOC (1.94 months; 95% CI: 1.84 to 3.94), with an HR of 0.423 (95% CI: 0.176 to 0.941). Significance cannot be inferred as the analysis was not powered for this (Table 23).[28]

A Kaplan–Meier plot of PFS is shown in Figure 14. Landmark PFS analyses were conducted at 3, 6, 12, and 18 months and [redacted] elacestrant at each timepoint (all results can be seen in Table 23). The 6- and 12-month PFS rates were [redacted] and [redacted]%, respectively, in the elacestrant arm vs. [redacted]% and [redacted]% in the SOC arm.[101]

Figure 14: Kaplan–Meier plot of PFS in patients with *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i (dual mutated) | Elacestrant vs. SOC | DCO 2nd September 2022



Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DCO, data cutoff; *ESR1*, oestrogen receptor 1 gene; *PIK3CA*, phosphatidylinositol 3 kinase; mPFS, median progression-free survival; SOC, standard of care
Source: Bardia (2023)[28]

Table 23: Blinded IRC-assessed PFS | Patients with *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i (dual mutated) | DCO 2nd September 2022

	Elacestrant N=27	SOC N=35
HR (95% CI) **p**	0.423 (0.176 to 0.941) -	
Median PFS months (95% CI)	5.45 (2.14 to 10.84)	1.94 (1.84 to 3.94)
Events, n (%) **Death** **Progression**	[redacted] ([redacted]) [redacted] ([redacted]) [redacted] ([redacted])	[redacted] ([redacted]) [redacted] ([redacted]) [redacted] ([redacted])
3-month PFS rate (95% CI)	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
6-month PFS rate (95% CI)	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
12-month PFS rate (95% CI)	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
18-month PFS rate (95% CI)	[redacted] ([redacted] to [redacted])	[redacted] ([redacted])

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; DCO, data cutoff; *ESR1*, oestrogen receptor 1 gene; HR, hazard ratio; IRC, imaging review committee; n, number of patients with the observed characteristic; N, total number in group; PFS, progression-free survival; *PIK3CA*, phosphatidylinositol 3 kinase; SOC, standard of care
Source: Bardia (2023)[28], EMERALD dual mutation population 12 month+ *post hoc* analysis *Data on File (2023)*[101]

B.2.7.3.2 Overall survival | Key secondary endpoint | DCO 2nd September 2022

At the time of the *post hoc* OS analysis, [redacted] ([redacted]) death events had occurred in the elacestrant group vs. [redacted] ([redacted]) in the SOC group. The HR for death in the elacestrant treatment group versus the SOC treatment group was [redacted] (95% CI: [redacted] to [redacted], [redacted]), see Table 24. There was a [redacted] median OS [redacted] seen with elacestrant ([redacted] months; 95% CI [redacted] to [redacted]) vs. SOC ([redacted] months; 95% CI: [redacted] to [redacted]). A Kaplan–Meier plot is shown in Figure 15.[101]

The numbers of patients with any individual reason for censoring were [redacted] across treatment groups; [redacted] patients ([redacted]%) in the elacestrant group vs. [redacted] patients ([redacted]%) in the SOC group – [redacted] ([redacted]%) vs. [redacted] ([redacted]%) censored as still in survival follow-up and [redacted] ([redacted]%) vs. [redacted] ([redacted]%) censored due to withdrawn consent for elacestrant vs. SOC respectively.[101]

Landmark analyses were conducted at 3, 6, 12, 18 and 24 months (Table 24) and the estimates [redacted] the elacestrant arm at each timepoint. The 6- and 12-month OS rates were [redacted]% and [redacted]%, respectively, in the elacestrant arm vs. [redacted]% and [redacted]% in the SOC arm.[101]

Figure 15: Kaplan–Meier plot for OS | Patients with *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i (dual mutated) | Elacestrant vs. SOC | DCO 2nd September 2022

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DCO, data cutoff; ELA, elacestrant; *ESR1*, oestrogen receptor 1 gene; OS, overall survival; *PIK3CA*, phosphatidylinositol 3 kinase; SOC, standard of care
Source: EMERALD dual mutation population 12 month+ *post hoc* analysis *Data on File (2023)*[101]

Table 24: OS | Patients with *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i (dual mutated) | DCO 2nd September 2022

	Elacestrant N=27	SOC N=35
HR (95% CI)	[redacted] ([redacted] to [redacted])	
p	[redacted]	
Median OS months (95% CI)	[redacted] ([redacted] – [redacted])	[redacted] ([redacted] – [redacted])
Events (death), n (%)	[redacted] ([redacted])	[redacted] ([redacted])
3-month OS rate (95% CI)	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
6-month OS rate (95% CI)	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
12-month OS rate (95% CI)	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
18-month OS rate (95% CI)	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
24-month OS rate (95% CI)	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; DCO, data cutoff; *ESR1*, oestrogen receptor 1 gene; HR, hazard ratio; n, number of patients with the observed characteristic; N, total number in group; OS, overall survival; *PIK3CA*, phosphatidylinositol 3 kinase; SOC, standard of care
Source: EMERALD dual mutation population 12 month+ *post hoc* analysis *Data on File (2023)*[101]

B.2.7.3.3 Patient-Reported Outcomes | DCO 8th July 2022

Overall, QoL was maintained between treatment groups and HRQoL data for the subgroup of patients with ESR1-mut, PIK3CA-mut and ≥12 months of prior ET + CDK4/6i (dual mutated) were consistent with those reported for All Patients and all patients with *ESR1-mut* (see Section B.2.6.4).

Mean (SD) EQ-5D-5L index scores at EOT were similar for elacestrant [redacted] ([redacted]) vs. SOC [redacted] ([redacted]), with no notable differences over time. Similarly, there was no meaningful mean (SD) change from baseline for either elacestrant [redacted] ([redacted]) or SOC [redacted] ([redacted]).[101] Please see Appendix E for further details.

B.2.7.3.4 Adverse reactions | Treatment compliance, exposure and most common TEAEs

Overall, safety data for the subgroup of patients with *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i (dual mutated) were consistent with those reported for All Patients and all patients with *ESR1-mut* (see Section B.2.10).

Most AEs were Grade 1 or 2, with very few Grade ≥3 events reported. At least one TEAE of any Grade was reported for [redacted] ([redacted]%) in the elacestrant arm and [redacted] ([redacted]%) in the SOC arm. The most common TEAEs reported for elacestrant were nausea ([redacted] [[redacted]%]), vomiting ([redacted] [[redacted]%]), and arthralgia ([redacted] [[redacted]%]). The most common TEAEs reported for SOC were anaemia ([redacted] [[redacted]%]), arthralgia ([redacted] [[redacted]%]), and nausea ([redacted] [[redacted]%]).[101] Please see Appendix E for further details.

B.2.8 Meta-analysis

There is only one relevant study (EMERALD) for the indicated population relevant to this submission, therefore a meta-analysis was not performed.

B.2.9 Indirect and mixed treatment comparisons

As the SLR (see Section B.2.1) did not identify any comparator efficacy data, the company had to explore potential sources of real-world evidence (RWE) to inform an ITC to compare efficacy between elacestrant and the comparators by utilising RWE and the EMERALD study. As the *ESR1-mut* is not currently tested for in the UK and Europe, it was necessary to explore RWE sources outside the UK and Europe, and the Flatiron real-world database (RWD) was considered.

Flatiron database

Flatiron is a RWD gathering clinical data from electronic health records filled by cancer care providers across the US. Two cohorts were considered:

- Patients ≥ 18 years of age with *ESR1-mut,* ER+/HER2- advanced/mBC, previously treated by CDK6/4i therapy for at least 12 months, receiving everolimus + exemestane
- Patients ≥ 18 years of age with *ESR1-mut*, *PIK3CA-mut,* ER+/HER2- advanced/mBC, previously treated by CDK6/4i therapy for at least 12 months, receiving alpelisib + fulvestrant

The inclusion criteria for the Flatiron cohort were aligned as much as possible with EMERALD to facilitate an appropriate match of patients:

- Chart confirmed diagnosis of breast cancer (with confirmed histology of tumour sample) assessed from Comprehensive Genomic Profiling (CGP) or based on International Classification of Disease (ICD-9-CM 174.x or 175.x or ICD-10-CM C50x)
- Women aged 50 years or older at index line start (as a proxy for post-menopause)
- Evidence of ER+/HER2- from -60 days before stage III unresectable/mBC
- Diagnosis date up to 28 days after the start date of index line
- Tested positive for *ESR1-mut* any time before or within 28 days after the start date of index line
- Patient has at least two clinical visits after January 1st, 2011
- Diagnosis at the stage III unresectable/stage IV or earlier diagnosis followed by the development of distant and recurrent mBC
- Evidence of treatment with ET in 1L and/or 2L
- Evidence of treatment with CDK6/4i therapy in 1L and/or 2L

- Received everolimus + exemestane or alpelisib + fulvestrant in 2L and/or 3L (index line)

The outputs available from Flatiron were:

- Aggregate patient characteristics
- OS: overall and stratified by CDK4/6i exposure time
- PFS: overall and stratified by CDK4/6i exposure time

Data from 32 patients receiving everolimus + exemestane were available for the *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population. For alpelisib + fulvestrant, data from 33 patients were available for the *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population. Data from these patients were used in the ITC to elacestrant for each population (patient characteristics presented in Table 26 and Table 28).

B.2.9.1 Methods

Owing to the absence of individual patient-level data (IPD) for the comparators and a lack of common comparator, an unanchored matching-adjusted indirect comparison (MAIC) was implemented to facilitate an ITC between elacestrant and everolimus + exemestane and between elacestrant and alpelisib + fulvestrant, for the relevant patient populations. Two MAICs were performed, where the elacestrant IPD from EMERALD were reweighted based on key patient characteristics to match the mean/median characteristics from Flatiron for each population considered. Four comparisons were subsequently made between OS and PFS for the *ESR1-mut* and ≥12 months of prior ET and CDK4/6i population, and *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET and CDK4/6i population using the weighted elacestrant data from EMERALD and comparator data from the Flatiron RWD.

To implement the approach of MAIC, a weight is calculated for each patient in the individual data from EMERALD based on matching to the comparator patient characteristics, with patients from the EMERALD trial who are better matched to the comparator patient characteristics given a higher weight than those who are not as well matched. Using the resultant weights, weighted outcomes are estimated for the elacestrant patients, effectively reweighting the available trial data to match the comparator.

The following steps were implemented to perform the MAIC:

- Apply inclusion criteria for the Flatiron RWD to EMERALD
- Identify prognostic factors and treatment effect modifiers to be included in the MAIC
- Estimation of the weights associated with each individual EMERALD patient through the generation of a logistic regression model based on a similar approach to propensity score weighting:

  $$log(\omega_i) = \alpha_0 + \alpha_1 X_i$$

  where X_i is the covariate vector for the i-th patient in the EMERALD trial and ω_i is the weight attributed to the i-th patient receiving elacestrant

- Comparison of weighted-elacestrant and comparator patient characteristics to ensure balanced populations have been achieved
- Outcomes of OS and PFS for elacestrant and the comparators compared and extracted for input to the cost-effectiveness model (see Section B.3.3.4)

Table 25 presents the prognostic factors and treatment effect modifiers identified by key opinion leaders (KOLs).

Table 25: Identified prognostic factors and treatment effect modifiers

Characteristic	Included in MAIC?	Comments
Age	Yes	Flatiron patients restricted to 50 years or older
Menopausal status	Partial	Included implicitly through a focus on postmenopausal women in EMERALD and older women in Flatiron
ECOG PS	No	Presence of ~25% unknown ECOG in Flatiron.
Number of metastatic sites	No	Excluded due to lack of data
Bone metastases / bone metastases only	No	Excluded due to lack of data
Visceral metastases	No	Excluded due to lack of data
Length of time on prior CDK4/6i	Partial	Included implicitly through population restriction (prior CDK4/6i ≥12 months)
Time since original diagnosis	No	Discrepancy in data available (only time since stage III diagnosis in Flatiron study)
ER expression	Partial	Included implicitly through population restriction (focus on *ESR1-mut)*
Histology (ductal vs. lobular)	No	Excluded due to lack of data
Prior chemotherapy	Yes	
Number of treatment lines in metastatic setting	Yes – for ET lines	Number of prior ET included as only number of prior lines of ET available
De novo vs. recurrent (i.e. diagnosed in adjuvant setting)	No	Excluded due to lack of data
De novo vs. progressed	No	Excluded due to lack of data

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; MAIC, matching-adjusted indirect comparison; PS, performance status.

Based on available data, the variables included in the MAIC for matching across populations were:

- Age
- Number of prior ET lines
- Prior chemotherapy status

Menopausal status was not explicitly available in Flatiron, however patients in Flatiron were restricted to women aged 50 years or older as a proxy intended to correspond with the postmenopausal population in the EMERALD trial. All patients in each population were female. There were approximately 25% of patients with unknown ECOG PS from the Flatiron

database for both populations. A sensitivity analysis was performed where the proportion of patients with unknown ECOG PS was redistributed to the known ECOG categories, with similar results observed to the base case.

B.2.9.2 Results

B.2.9.2.1 *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population

Table 26 presents the unweighted elacestrant, MAIC-weighted elacestrant and everolimus + exemestane patient characteristics. The effective sample size (ESS) for elacestrant was [redacted] after weighting ([redacted] of the initial sample size). No extreme individual was identified based on the weights.

Table 26: Comparison of patient characteristics after weighting | *ESR1-mut* and ≥12 months of prior ET and CDK4/6i population

Characteristic		Elacestrant		Everolimus + exemestane
		Unweighted	Weighted	
N / ESS		78	[redacted]	32
Age	Mean (SD)	[redacted]	[redacted]	[redacted]
Sex, n (%)	Male	[redacted]	[redacted]	[redacted]
	Female	[redacted]	[redacted]	[redacted]
ECOG PS, n (%)	ECOG 0	[redacted]	[redacted]	[redacted]
	ECOG 1	[redacted]	[redacted]	[redacted]
	ECOG 2	[redacted]	[redacted]	[redacted]
	ECOG 3	[redacted]	[redacted]	[redacted]
	Unknown	[redacted]	[redacted]	[redacted]
Lines of prior ET	1	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]
Prior chemotherapy in an advance/metastatic setting	Yes (%)	[redacted]	[redacted]	[redacted]
	No (%)	[redacted]	[redacted]	[redacted]

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ECOG, Eastern Cooperative Oncology Group; *ESR1*, oestrogen receptor 1 gene; ESS, effective sample size; ET, endocrine therapy; PS, performance status; SD, standard deviation.

Figure 16 and Figure 17 present the unweighted and MAIC-weighted OS and PFS for elacestrant and everolimus + exemestane. The analyses show [redacted] PFS for patients treated with elacestrant compared to those treated with everolimus + exemestane. Crossing of curves is observed in both plots, indicating the proportional hazards assumption may not hold. As such, independent parametric survival models fitted to the OS and PFS data for weighted-elacestrant and everolimus + exemestane (see Section B.3.3.4) were preferred over applying the MAIC HRs to the elacestrant outcomes.

Figure 16: Unweighted and MAIC-weighted OS | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ESR1, oestrogen receptor 1 gene; ET, endocrine therapy; EVER, everolimus; exem, exemestane; MAIC, matching-adjusted indirect comparison; OS, overall survival.

Figure 17: Unweighted and MAIC-weighted PFS | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ESR1, oestrogen receptor 1 gene; ET, endocrine therapy; EVER, everolimus; exem, exemestane; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival.

For completeness, Table 27 presents median OS and PFS, and MAIC-weighted HRs for elacestrant versus everolimus + exemestane. Elacestrant is observed to be associated with [redacted] OS and PFS compared to everolimus + exemestane.

Table 27: MAIC hazard ratios | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population

Comparison (elacestrant versus)	Median (95% CI)		Elacestrant vs. EVE + EXE HR (95% CI)
	Elacestrant weighted	Everolimus + exemestane	
OS	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])	0.64 (0.35, 1.16)
PFS	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])	0.59 (0.36, 0.96)

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; EVE, everolimus; EXE, exemestane; HR, hazard ration; MAIC, matching-adjusted indirect comparison; NR, not reported; OS, overall survival; PFS, progression-free survival.

B.2.9.2.2 *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population

Table 28 presents the unweighted elacestrant, MAIC-weighted elacestrant and alpelisib + fulvestrant patient characteristics. The effective sample size (ESS) for elacestrant was [redacted] after weighting ([redacted] of the initial sample size). No extreme individual was identified based on the weights.

Table 28: Comparison of patient characteristics after weighting | *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population

Characteristic		Elacestrant		Alpelisib + fulvestrant
		Unweighted	Weighted	
N / ESS		27	[redacted]	33
Age	Mean (SD)	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])
Sex, n (%)	Male	[redacted] ([redacted])	[redacted]	[redacted] ([redacted])
	Female	[redacted] ([redacted])	[redacted]	[redacted] ([redacted])
ECOG PS, n (%)	ECOG 0	[redacted] ([redacted])	[redacted]	[redacted] ([redacted])
	ECOG 1	[redacted] ([redacted])	[redacted]	[redacted] ([redacted])
	ECOG 2	[redacted] ([redacted])	[redacted]	[redacted] ([redacted])
	ECOG 3	[redacted] ([redacted])	[redacted]	[redacted] ([redacted])
	Unknown	[redacted] ([redacted])	[redacted]	[redacted] ([redacted])
Lines of prior ET	1	[redacted] ([redacted])	[redacted]	[redacted] ([redacted])
	2	[redacted] ([redacted])	[redacted]	[redacted] ([redacted])
Prior chemotherapy in an advance/metastatic setting	Yes (%)	[redacted] ([redacted])	[redacted]	[redacted] ([redacted])
	No (%)	[redacted] ([redacted])	[redacted]	[redacted] ([redacted])

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ECOG, Eastern Cooperative Oncology Group; *ESR1*, oestrogen receptor 1 gene; ESS, effective sample size; ET, endocrine therapy; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PS, performance status; SD, standard deviation.

Figure 18 and Figure 19 present the unweighted and MAIC-weighted OS and PFS for elacestrant and alpelisib + fulvestrant. The analyses show [redacted] PFS for patients treated with elacestrant and alpelisib + fulvestrant. For OS, [redacted]

[redacted]. Similar to the comparison with everolimus + exemestane, the crossing of curves is observed. As such, independent parametric survival models fitted to the OS and PFS data for weighted-elacestrant and alpelisib + fulvestrant (see Section B.3.3.4) was preferred over applying the MAIC HRs to the elacestrant outcomes.

Figure 18: Unweighted and MAIC-weighted OS | *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population

Abbreviations: ALP, alpelisib; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ESR1, oestrogen receptor 1 gene; ET, endocrine therapy; fulv, fulvestrant; MAIC, matching-adjusted indirect comparison; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; OS, overall survival.

Figure 19: Unweighted and MAIC-weighted PFS | *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population

Abbreviations: ALP, alpelisib; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ESR1, oestrogen receptor 1 gene; ET, endocrine therapy; fulv, fulvestrant; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

For completeness, Table 29 presents median OS and PFS, and the MAIC-weighted HRs for elacestrant versus alpelisib + fulvestrant. Elacestrant is associated with [redacted] median OS and PFS than alpelisib.

Table 29: MAIC hazard ratios | *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population

Comparison (elacestrant versus)	Median (95% CI)		Elacestrant vs. ALP + FUL HR (95% CI)
	Elacestrant weighted	Alpelisib + fulvestrant	
OS	[redacted] ([redacted], [redacted])	[redacted] ([redacted], [redacted])	0.80 (0.33, 1.92)
PFS	[redacted] ([redacted], [redacted])	[redacted] ([redacted], [redacted])	1.05 (0.50, 2.20)

Abbreviations: ALP, alpelisib; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; FUL, fulvestrant; HR, hazard ration; MAIC, matching-adjusted indirect comparison; NR, not reached; OS, overall survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PFS, progression-free survival.

B.2.9.3 Uncertainties in the indirect and mixed treatment comparisons

The EMERALD study and Flatiron RWD differ in terms of study type and design. EMERALD is an RCT, with defined timelines and visits in which to measure outcomes (e.g., scans every two months), whereas Flatiron is a RWD with outcomes collected in real-time. As such, the studies differ in terms of the approach to data collection.

A further uncertainty is borne from the MAIC implicit assumption of similarity between the EMERALD study and Flatiron RWD. The methodology assumes a reasonable level of overlap which is somewhat captured by the reported patient characteristics however, some of the prognostic factors and treatment effect modifiers identified by KOLs were missing and thus, could not be compared across evidence bases. However, the MAIC approach implemented attempts to mitigate this limitation as much as possible, by applying the inclusion/exclusion criteria of Flatiron to EMERALD, and by including all possible terms available into the matching regression to achieve a more robust comparison of outcomes compared to a naïve comparison approach.

The final limitation is the relatively low patient numbers available for the comparators in the relevant patient populations from Flatiron. In particular, the small sample size means the tails of the KM curves should be interpreted with caution. Despite low numbers, the evidence from Flatiron is the most relevant data identified to inform a comparison of efficacy with elacestrant, owing to alignment of patient populations and the treatment regimens received by patients in the database.

B.2.10 Adverse reactions

The safety data presented are from the safety population of the EMERALD trial, defined as all patients who received ≥1 dose of study drug, both for All Patients and patients with *ESR1-mut*. The safety population for All Patients consisted of 237 (99.2%) patients in the elacestrant arm and 230 (96.2%) patients in the SOC arm. The safety population for patients with *ESR1-mut* consisted of 115 (100%) patients in the elacestrant arm and 106 (93.8%) patients in the SOC arm. All TEAEs reported are based on the 6th of September 2021 DCO.[98]

B.2.10.1 Treatment compliance and exposure

The two treatment arms received a similar relative dose intensity (RDI), but the duration of treatment was longer for the elacestrant arm vs. SOC. Compliance was similar across the treatment arms and exposure among All Patients was similar to that as for the patients with *ESR1-mut* (Table 30).[98]

Among patients with *ESR1-mut*, mean (SD) duration of treatment was longer in the elacestrant group at [redacted] days ([redacted]) vs. the SOC group. Almost all patients with *ESR1-mut* ([redacted] [[redacted]%]) in the elacestrant arm received an RDI of [redacted].[98]

Table 30: Exposure to study treatment | Safety population | DCO 6th September 2021

	All patients			Patients with *ESR1-mut*		
	Elacestrant N=237	SOC (fulvestrant) N=162	SOC (AIs) N=68	Elacestrant N=115	SOC (fulvestrant) N=79	SOC (AIs) N=27
Duration on treatment (days)						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Compliance (%)						
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative dose intensity, n (%)						
≤50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>50 to ≤75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>75 to ≤90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>90 to ≤100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: Duration on treatment for elacestrant and AIs was calculated as (last dose date – first dose date +1). Duration on treatment for fulvestrant was calculated as (end date of last cycle – first dose date +1). Compliance for elacestrant and AIs was calculated as total number of doses divided by duration on treatment. Compliance for fulvestrant was calculated as total number of doses divided by total number of intended doses. Relative dose intensity was calculated as absolute dose intensity divided by planned dose intensity *100.

Abbreviations: AI, aromatase inhibitor; DCO, data cutoff; *ESR1*, oestrogen receptor 1 gene; max, maximum; min, minimum; n, number of patients with the observed characteristic; N, total number of patients in group; SD, standard deviation; SOC, standard of care
Source: EMERALD CSR *Data on File* (2023)[98]

B.2.10.2 TEAEs | DCO 6th September 2021

Among patients with *ESR1-mut*, TEAEs – whether related to elacestrant therapy or not – were reported in 105 patients (91.3%) in the elacestrant group and 92 patients (86.8%) in the SOC group. A higher proportion of events were deemed to be treatment related in the elacestrant group (71 [61.7%]) than the SOC group (49 (46.2%]). Although numbers were generally low, there were more Grade ≥3 TEAEs in the elacestrant group (32 [27.8%]) than the SOC group (23 [21.7%]), but very few of these were deemed to be treatment related (<10% across all groups and treatment arms). A similar proportion of serious TEAEs were reported across the two treatment arms (14 [12.2%] for elacestrant vs. 12 [11.3%] for SOC). None were deemed to be treatment related in the SOC arm, and only 2 (1.7%) were treatment related in the elacestrant arm. More patients in the elacestrant group had TEAES leading to dose interruption (25 [21.7%]), dose reduction (6 [5.2%]) and discontinuation (6 [5.2%]) than the SOC arm (7 [6.6%], 0 and 4 [3.8%], respectively), but the numbers were low regardless of treatment and very few were deemed to be treatment related. There were 4 on-study deaths in the patients with *ESR1-mut* (3 on elacestrant and 1 on SOC), but none of these were thought to be treatment related. Patterns of TEAEs observed in patients with *ESR1-mut* were similar to those observed in All Patients (see Table 31 for full results).[98]

Table 31: Overall Summary of TEAEs | Safety population | DCO 6th September 2021

	All patients		Patients with *ESR1-mut*	
TEAE Type, n (%)	**Elacestrant N=237**	**SOC N=230**	**Elacestrant N=115**	**SOC N=106**
TEAE				
○ Any	218 (92.0)	198 (86.1)	105 (91.3)	92 (86.8)
○ Related	150 (63.3)	100 (43.5)	71 (61.7)	49 (46.2)
Grade ≥3				
○ Any	64 (27.0)	48 (20.9)	32 (27.8)	23 (21.7)
○ Related	17 (7.2)	7 (3.0)	10 (8.7)	5 (4.7)
Serious AE				
○ Any	29 (12.2)	25 (10.9)	14 (12.2)	12 (11.3)
○ Related	3 (1.3)	0	2 (1.7)	0
Fatal events				
○ Any	4 (1.7)	6 (2.6)	3 (2.6)	1 (0.9)
○ Related	0	0	0	0
AE leading dose interruption				
○ Any	36 (15.2)	12 (5.2)	25 (21.7)	7 (6.6)
○ Related	15 (6.3)	4 (1.7)	9 (7.8)	3 (2.8)

AE leading to dose reduction				
○ Any	7 (3.0)	0	6 (5.2)	0
○ Related	6 (2.5)	0	5 (4.3)	0
AE leading to discontinuation				
○ Any	15 (6.3)	10 (4.3)	6 (5.2)	4 (3.8)
○ Related	8 (3.4)	2 (0.9)	5 (4.3)	2 (1.9)

Footnotes: MedDRA version 23.0, CTCAE version 5.0. If a patient experienced more than 1 event in a given category, that patient is counted only once in that category.
Abbreviations: AE, adverse event; DCO, data cutoff; *ESR1*, oestrogen receptor 1 gene; n, number of patients with the observed characteristic; N, total number of patients in group; SOC, standard of care; TEAE, treatment-emergent adverse event
Source: EMERALD CSR *Data on File* (2023)[98]

B.2.10.2.1 Most common TEAEs

In patients with *ESR1-mut*, at least one TEAE of any Grade was reported for 105 (91.3%) patients in the elacestrant arm and 92 (86.8%) in the SOC arm. The most common TEAEs reported for elacestrant were nausea (40 [34.8%]), arthralgia (23 [20%]), vomiting (21 [18.3%]), fatigue (20 [17.4%]), decreased appetite (19 [16.5%]), diarrhoea (17 [14.8%]), back pain (16 [13.9%]) and headache (15 [13.0%]). The most common TEAEs reported for SOC were fatigue (21 [19.8%]), nausea (19 [17.9%]), arthralgia (19 [17.9%]), increased aspartate aminotransferase (15 [14.2%]), diarrhoea (13 [12.3%]), increased alanine aminotransferase (13 [12.3%]), headache (11 [10.4%]) and anaemia (11 [10.4%]). Understandably, injection site pain was only reported for those on SOC as only fulvestrant was injected. No AEs of bradycardia/sinus bradycardia or QTc prolongation were reported in the elacestrant arm, both of which are common AEs observed in studies of other novel antiestrogens.[116–118] In general, the safety profile of elacestrant and SOC in the *ESR1-mut* group was similar to that observed in the All Patients group.[98]

At least one TRAE of any Grade was reported for 71 (61.7%) patients in the elacestrant arm and 49 (46.2%) in the SOC arm. The most common TRAEs for elacestrant were nausea (26 [22.6%]), fatigue (14 [12.2%]), decreased appetite (11 [9.6%]) and vomiting (11 [9.6%]). The most common TRAEs for SOC were nausea (12 [12.3%]), fatigue (12 [11.3%]), arthralgia (9 [8.5%]) and injection site pain (8 [7.5%]). Patterns of TRAE observed in patients with *ESR1-mut* were similar to those observed in All Patients (see Table 32 for full results).[98]

Table 32: Any TEAEs and TRAEs in ≥5% patients in All Patients group and patients with *ESR1-mut* | Safety population | DCO 6th September 2021

System organ class Preferred term, n (%)	All patients				Patients with *ESR1-mut*			
	Elacestrant N=237		SOC N=230		Elacestrant N=115		SOC N=106	
	Any	Related	Any	Related	Any	Related	Any	Related
Any TEAEs	218 (92.0)	150 (63.3)	198 (86.1)	100 (43.5)	105 (91.3)	71 (61.7)	92 (86.8)	49 (46.2)
○ Nausea	83 (35.0)	60 (25.3)	44 (19.1)	20 (8.7)	40 (34.8)	26 (22.6)	19 (17.9)	13 (12.3)
○ Arthralgia	34 (14.3)	9 (3.8)	37 (16.1)	18 (7.8)	23 (20.0)	5 (4.30)	19 (17.9)	9 (8.5)
○ Vomiting	45 (19.0)	26 (11.0)	20 (8.7)	6 (2.6)	21 (18.3)	11 (9.6)	10 (9.4)	5 (4.7)
○ Fatigue	45 (19.0)	26 (11.0)	44 (19.1)	18 (7.8)	20 (17.4)	14 (12.2)	21 (19.8)	12 (11.3)
○ Decreased appetite	35 (14.8)	18 (7.6)	22 (9.6)	7 (3.0)	19 (16.5)	11 (9.6)	8 (7.5)	3 (2.8)
○ Diarrhoea	33 (13.9)	18 (7.6)	23 (10.0)	8 (3.5)	17 (14.8)	9 (7.8)	13 (12.3)	6 (5.7)
○ Back pain	33 (13.9)	1 (0.4)	22 (9.6)	0 (0.0)	16 (13.9)	-	9 (8.5)	-
○ Headache	29 (12.2)	10 (4.2)	26 (11.3)	10 (4.3)	15 (13.0)	6 (5.2)	11 (10.4)	4 (3.8)
○ Dyspepsia	24 (10.1)	14 (5.9)	6 (2.6)	2 (0.9)	13 (11.3)	9 (7.8)	3 (2.8)	2 (1.9)
○ Insomnia	18 (7.6)	6 (2.5)	11 (4.8)	5 (2.2)	13 (11.3)	4 (3.5)	7 (6.6)	4 (3.8)
○ Constipation	29 (12.2)	11 (4.6)	15 (6.5)	2 (0.9)	12 (10.4)	5 (4.3)	8 (7.5)	1 (0.9)
○ Aspartate aminotransferase increased	31 (13.1)	7 (3.0)	29 (12.6)	8 (3.5)	12 (10.4)	4 (3.5)	15 (14.2)	5 (4.7)
○ Asthenia	22 (9.3)	11 (4.6)	19 (8.3)	7 (3.0)	11 (9.6)	5 (4.3)	9 (8.5)	5 (4.7)
○ Anaemia	22 (9.3)	8 (3.4)	17 (7.4)	4 (1.7)	11 (9.6)	5 (4.3)	11 (10.4)	3 (2.8)
○ Hot flush	27 (11.4)	23 (9.7)	19 (8.3)	14 (6.1)	11 (9.6)	10 (8.7)	8 (7.5)	6 (5.7)
○ Pain in extremity	18 (7.6)	2 (0.8)	14 (6.1)	3 (1.3)	10 (8.7)	1 (0.9)	5 (4.7)	2 (1.9)

○ Blood cholesterol increased	16 (6.8)	6 (2.5)	7 (3.0)	3 (1.3)	9 (7.8)	5 (4.3)	3 (2.8)	0 (0.0)
○ Blood alkaline phosphatase increased	15 (6.3)	4 (1.7)	17 (7.4)	4 (1.7)	8 (7.0)	2 (1.7)	7 (6.6)	2 (1.9)
○ Dyspnoea	18 (7.6)	0 (0.0)	16 (7.0)	1 (0.4)	8 (7.0)	0 (0.0)	7 (6.6)	1 (0.9)
○ Urinary tract infection	16 (6.8)	2 (0.8)	12 (5.2)	0 (0.0)	8 (7.0)	1 (0.9)	6 (5.7)	0 (0.0)
○ Bone pain	15 (6.3)	3 (1.3)	15 (6.5)	2 (0.9)	6 (5.2)	1 (0.9)	5 (4.7)	1 (0.9)
○ Musculoskeletal chest pain	14 (5.9)	0 (0.0)	7 (3.0)	1 (0.4)	6 (5.2)	0 (0.0)	2 (1.9)	1 (0.9)
○ Oedema peripheral	9 (3.8)	1 (0.4)	5 (2.2)	1 (0.4)	6 (5.2)	1 (0.9)	2 (1.9)	0 (0.0)
○ Pyrexia	8 (3.4)	-	5 (2.2)	-	6 (5.2)	-	3 (2.8)	-
○ Alanine aminotransferase increased	22 (9.3)	5 (2.1)	24 (10.4)	6 (2.6)	6 (5.2)	0 (0.0)	13 (12.3)	5 (4.7)
○ Dizziness	10 (4.2)	6 (2.5)	4 (1.7)	1 (0.4)	6 (5.2)	4 (3.5)	1 (0.9)	0 (0.0)
○ Cough	15 (6.3)	2 (0.8)	12 (5.2)	0 (0.0)	6 (5.2)	1 (0.9)	6 (5.7)	0 (0.0)
○ Lymphocyte count decreased	12 (5.1)	6 (2.5)	5 (2.2)	2 (0.9)	5 (4.3)	2 (1.7)	2 (1.9)	1 (0.9)
○ Abdominal pain	15 (6.3)	4 (1.7)	14 (6.1)	4 (1.7)	5 (4.3)	3 (2.6)	7 (6.6)	4 (3.8)
○ Musculoskeletal pain	11 (4.6)	0 (0.0)	13 (5.7)	7 (3.0)	5 (4.3)	0 (0.0)	10 (9.4)	6 (5.7)
○ Blood pressure increased	9 (3.8)	2 (0.8)	12 (5.2)	2 (0.9)	5 (4.3)	0 (0.0)	5 (4.7)	1 (0.9)
○ Blood glucose increased	6 (2.5)	-	12 (5.2)	-	5 (4.3)	-	5 (4.7)	-
○ Myalgia	11 (4.6)	2 (0.8)	17 (7.4)	12 (5.2)	4 (3.5)	2 (1.7)	6 (5.7)	5 (4.7)
○ Injection site pain	0 (0.0)	0 (0.0)	14 (6.1)	13 (5.7)	0 (0.0)	0 (0.0)	9 (8.5)	8 (7.5)

Footnotes: MedDRA version 23.0. Patients with one or more AEs within a System Organ Class of MedDRA are counted only once. Preferred terms are summarised using AE Synonym Terms.
Abbreviations: DCO, data cutoff; *ESR1*, oestrogen receptor 1 gene; n, number of patients with the observed characteristic; N, total number of patients in group; SOC, standard of care; TEAE, treatment-emergent adverse event
Source: EMERALD CSR *Data on File* (2023)[98]

B.2.10.2.2 Grade 3 or 4 TEAEs

AEs in both treatment arms were mainly Grade 1 and 2. The incidence of Grade 3 or 4 AEs was low in both treatment arms with none exceeding 5%. Table 33 shows the Grade 3 and Grade 4 TEAEs that exceeded ≥2%; (32 [27.8%] for elacestrant and 23 [21.7%] for SOC in patients with *ESR1-mut*).[98]

Patients taking elacestrant had a higher incidence of treatment-related Grade 3 and Grade 4 TEAEs than SOC, although numbers were low in both treatment groups; (17 [7.2%] vs. 7 [3.0%] for All Patients and 10 [8.7%] vs. 5 [4.7%] for patients with *ESR1-mut*). No individual TEAE had a frequency of ≥2% in the SOC arm, and only nausea had a frequency of ≥2% for elacestrant, which was reported in 3 patients with *ESR1-mut* (2.6%).[98]

Table 33: Grade 3 or 4 TEAEs in ≥2% of All Patients or patients with *ESR1-mut* | Safety population | DCO 6th September 2021

System organ class Preferred term, n (%)	All patients		Patients with *ESR1-mut*	
	Elacestrant N=237	SOC N=230	Elacestrant N=115	SOC N=106
Patients with any Grade 3 or 4 TEAEs	64 (27.0)	48 (20.9)	32 (27.8)	23 (21.7)
○ Nausea	6 (2.5)	2 (0.9)	5 (4.3)	1 (0.9)
○ Back pain	6 (2.5)	1 (0.4)	5 (4.3)	0
○ Bone pain	6 (2.5)	1 (0.4)	3 (2.6)	1 (0.9)
○ Asthenia	4 (1.7)	2 (0.9)	3 (2.6)	1 (0.9)
○ Anaemia	4 (1.7)	5 (2.2)	2 (1.7)	2 (1.9)
○ Alanine aminotransferase increased	5 (2.1)	1 (0.4)	1 (0.9)	0
○ Blood pressure increased	5 (2.1)	6 (2.6)	1 (0.9)	2 (1.9)
○ Neutropenia	0	3 (1.3)	0	3 (2.8)

Footnotes: MedDRA version 23.0, CTCAE version 5.0. Patients with one or more AEs within a System Organ Class of MedDRA are counted only once. Preferred Terms are summarised using AE Synonym Terms
Abbreviations: DCO, data cutoff; *ESR1*, oestrogen receptor 1 gene; n, number of patients with the observed characteristic; N, total number of patients in group; SOC, standard of care; TEAE, treatment-emergent adverse event
Source: EMERALD CSR *Data on File* (2023)[98]

B.2.10.2.3 TEAEs associated with changes in treatment (in ≥1% of patients)

As per the prescribing information, no dose reduction was allowed for AIs and was only allowed for fulvestrant in cases of liver impairment. As such, TEAEs leading to dose reduction were reported for 6 patients with *ESR1-mut* on elacestrant (5.2%) vs. none on SOC.[98]

Among patients with *ESR1-mut*, a higher rate of dose interruption was recorded with elacestrant than SOC (25 [21.7%] vs. 7 [6.6%]). On SOC, no individual TEAE was reported as the reason for dose interruption in ≥2% of patients. Nausea was the only TEAE that led to

dose interruption on elacestrant in ≥2% of patients (5 patients [4.3%]). Patterns of TEAEs observed in patients with *ESR1-mut* were similar to those observed in All Patients (see Table 34). TRAEs leading to dose interruption occurred in 9 patients (7.8%) on elacestrant and 3 patients (2.8%) on SOC – two individual TEAEs were deemed treatment related with a frequency ≥1% in the elacestrant arm (nausea in 3 [2.6%] and fatigue in 2 [1.7%]), but none in the SOC arm. Again, patterns observed in patients with *ESR1-mut* were similar to those observed in All Patients, with TRAEs leading to dose interruption in 15 (6.3%) patients on elacestrant and 4 (1.7%) on SOC – none with a frequency ≥1% in the SOC arm, and only nausea in the elacestrant arm for 5 (2.1%) patients.[98]

TEAEs leading to premature study drug discontinuation were similar for elacestrant vs. SOC in patients with *ESR1-mut* (6 [5.2%] vs. 4 [3.8%]). None were reported in ≥2% of patients (Table 35). The frequency of TRAEs leading to discontinuation was very low across both patient groups for elacestrant vs. SOC (8 [3.4%] vs. 2 [0.9%] in All Patients and 5 [4.3%] vs. 2 [1.9%] in patients with *ESR1*-mut). No individual TEAEs occurred at a frequency of ≥1% in the SOC arm, but in the elacestrant arm nausea was reported in 3 (1.3%) for All Patients and decreased appetite in 2 (1.7%) for patients with *ESR1-mut*.[98]

Table 34: TEAEs leading to dose interruption in ≥1% patients with *ESR1-mut* | Safety population with *ESR1-mut* | DCO 6th September

System organ class Preferred term, n (%)	All patients		Patients with *ESR1-mut*	
	Elacestrant N=237	SOC N=230	Elacestrant N=115	SOC N=106
Any TEAE leading to interruption	36 (15.2)	12 (5.2)	25 (21.7)	7 (6.6)
○ Nausea	8 (3.4)	2 (0.9)	5 (4.3)	1 (0.9)
○ Vomiting	3 (1.3)	2 (0.9)	2 (1.7)	1 (0.9)
○ Bone pain	3 (1.3)	0	2 (1.7)	0
○ Fatigue	2 (0.8)	0	2 (1.7)	0
○ COVID-19	3 (1.3)	0	2 (1.7)	0
○ Alanine aminotransferase increased	3 (1.3)	0	1 (0.9)	0
○ Abdominal pain upper	3 (1.3)	0	1 (0.9)	0
○ Decreased appetite	2 (0.8)	3 (1.3)	1 (0.9)	2 (1.9)

Footnotes: MedDRA version 23.0. Patients with one or more AEs within a System Organ Class of MedDRA are counted only once. Preferred Terms are summarised using AE Synonym Terms
Abbreviations: DCO, data cutoff; *ESR1*, oestrogen receptor 1 gene; n, number of patients with the observed characteristic; N, total number of patients in group; SOC, standard of care; TEAE, treatment-emergent adverse event
Source: EMERALD CSR *Data on File* (2023)[98]

Table 35: TEAEs leading to treatment discontinuation in ≥1% patients with *ESR1-mut* | Safety population with *ESR1-mut* | DCO 6th September 2021

System organ class Preferred term, n (%)	All patients		Patients with *ESR1-mut*	
	Elacestrant N=237	SOC N=230	Elacestrant N=115	SOC N=106
Any TEAEs leading to discontinuation of study drug	15 (6.3)	10 (4.3)	6 (5.2)	4 (3.8)
○ Decreased appetite	2 (0.8)	0	2 (1.7)	0
○ Nausea	3 (1.3)	0	1 (0.9)	0
○ Aspartate aminotransferase increased	1 (0.4)	2 (0.9)	0	2 (1.9)
○ Alanine aminotransferase increased	0	2 (0.9)	0	2 (1.9)

Footnotes: MedDRA version 23.0. Patients with one or more AEs within a System Organ Class of MedDRA are counted only once. Preferred Terms are summarised using AE Synonym Terms.
Abbreviations: DCO, data cutoff; *ESR1*, oestrogen receptor 1 gene; n, number of patients with the observed characteristic; N, total number of patients in group; SOC, standard of care; TEAE, treatment-emergent adverse event
Source: EMERALD CSR *Data on File* (2023)[98]

B.2.10.3 Deaths and SAEs

B.2.10.3.1 On-study deaths

Deaths were considered to be TEAEs of CTCAE Grade 5. Overall, numbers were very low (see Table 36 for full results) with only 4 reported amongst patients with *ESR1-mut* (3 [2.6%] on elacestrant and 1 [0.9%)] on SOC). The incidence of treatment-emergent Grade 5 AEs was too low to determine any pattern and no deaths were assessed as study drug-related.[98]

Table 36: TEAEs with an outcome of death in All Patients and patients with *ESR1-mut* | Safety population | DCO 6th September 2021

System organ class Preferred term, n (%)	All patients		Patients with *ESR1-mut*	
	Elacestrant N=237	SOC N=230	Elacestrant N=115	SOC N=106
Patients with any TEAEs of CTCAE Grade 5	4 (1.7)	6 (2.6)	3 (2.6)	1 (0.9)
○ Diverticulitis	1 (0.4)	0	1 (0.9)	0
○ Septic shock	1 (0.4)	0	1 (0.9)	0
○ Cardiac arrest	1 (0.4)	0	1 (0.9)	0
○ COVID-19	0	1 (0.4)	0	1 (0.9)

○ Gastric perforation	0	1 (0.4)	-	-
○ Ischemic stroke	0	1 (0.4)	-	-
○ Pneumonia	0	1 (0.4)	-	-
○ Antiphospholipid syndrome	1 (0.4)	0	-	-
○ Arrhythmia	0	1 (0.4)	-	-
○ Myocardial infarction	0	1 (0.4)	-	-

Footnotes: MedDRA version 23.0, CTCAE version 5.0. Patients with one or more AEs within a System Organ Class of MedDRA are counted only once. Preferred Terms are summarised using AE Synonym Terms
Abbreviations: DCO, data cutoff; *ESR1*, oestrogen receptor 1 gene; n, number of patients with the observed characteristic; N, total number of patients in group; SOC, standard of care; TEAE, treatment-emergent adverse event
Source: EMERALD CSR *Data on File* (2023)[98]

B.2.10.3.2 Serious TEAEs

A similar proportion of serious TEAEs were reported across the two treatment arms for patients with *ESR1-mut* (14 [12.2%] for elacestrant vs. 12 [11.3%] for SOC). None of the reported serious AEs had an incidence that was ≥2%, therefore Table 37 reports those with a frequency ≥1%. Findings were similar to those for All Patients. No serious TEAEs were thought to be treatment related in the SOC arm, but 3 (1.3%) and 2 (1.7%) were thought to be related to elacestrant in All Patients and patients with *ESR1-mut*, respectively.[98]

Table 37: Serious TEAEs in ≥1% of patients with *ESR1-mut* | Safety population with *ESR1-mut* | DCO 6th September 2021

System organ class Preferred term, n (%)	All patients		Patients with *ESR1-mut*	
	Elacestrant N=237	SOC N=230	Elacestrant N=115	SOC N=106
Patients with any serious TEAEs	29 (12.2)	25 (10.9)	14 (12.2)	12 (11.3)
○ Nausea	3 (1.3)	0	2 (1.7)	0
○ Vomiting	2 (0.8)	0	2 (1.7)	0
○ Pneumonia	1 (0.4)	3 (1.3)	1 (0.9)	1 (0.9)
○ Abdominal pain	0	2 (0.9)	0	2 (1.9)
○ Urinary tract infection	0	2 (0.9)	0	2 (1.9)

Footnotes: MedDRA version 23.0. Patients with one or more AEs within a System Organ Class of MedDRA are counted only once. Preferred Terms are summarised using AE Synonym Terms
Abbreviations: DCO, data cutoff; *ESR1*, oestrogen receptor 1 gene; n, number of patients with the observed characteristic; N, total number of patients in group; SOC, standard of care; TEAE, treatment-emergent adverse event
Source: EMERALD CSR *Data on File* (2023)[98]

B.2.10.4 Safety conclusions

During the treatment period for EMERALD, elacestrant showed a predictable and manageable safety profile that is consistent with other ETs.[33] Mean (SD) duration of treatment was longer in the elacestrant group ([redacted] days [redacted]) than the SOC group ([redacted] days [redacted] for fulvestrant and [redacted] days [redacted] for AIs), for patients with *ESR1-mut.* Almost all patients with *ESR1-mut* ([redacted] [redacted%]) in the elacestrant arms received an RDI of [redacted]. The safety profile for patients with *ESR1-mut* and All Patients was generally similar.

AEs in both treatment arms were mainly Grade 1 and 2. The incidence of Grade 3 or 4 AEs was low in both treatment arms, reported in 32 (27.8%) of the elacestrant group and 23 (21.7%) of the SOC group among patients with *ESR1-mut*. No individual event had an incidence of Grade 3 and Grade 4 that exceeded 5%. Of those that were deemed treatment related (10 [8.7%] vs. 5 [4.7%]), no individual event had a frequency of ≥2% in the SOC arm and only nausea for elacestrant, was reported in 3 patients (2.6%).[98]

Among patients with *ESR1-mut*, there was a similar rate of TEAEs reported for elacestrant and SOC, irrespective of relationship to trial therapy (105 [91.3%] for elacestrant and 92 [86.8%] for SOC).[98] The four most common TEAEs reported for elacestrant and SOC included nausea (34.8% vs. 17.9%), arthralgia (20% vs. 17.9%) vomiting (18.3% vs. 9.4%) and fatigue (17.4% vs. 19.8%).[98] SOC had higher rates of increased aspartate aminotransferase (14.2% vs. 10.4%) and alanine aminotransferase (12.3% vs. 5.2%) and injection site pain was only reported for those on SOC.[98] No AEs of bradycardia/sinus bradycardia or QTc prolongation were reported in the elacestrant arm, both of which are common AEs observed in studies of other novel antiestrogens.[116–118] A higher proportion of TEAEs was deemed to be treatment related in the elacestrant group (71 [61.7%]) than the SOC group (49 [46.2%]). The most common TRAEs reported for both elacestrant and SOC were nausea (22.6% vs. 12.3%) and fatigue (12.2% vs. 11.3%].[98]

As per the prescribing information, no dose reduction was allowed for AIs, and was only allowed for fulvestrant in cases of liver impairment. As such, TEAEs leading to dose reduction were reported for 6 patients (5.2%) on elacestrant vs. none in the SOC arm. A higher rate of dose interruption was recorded with elacestrant than SOC (25 [21.7%] vs. 7 [6.6%]), but only one TEAE (nausea) was reported as the reason for the interruption in ≥2% of patients for elacestrant (5 [4.3%]). The rate of AEs leading to premature study drug discontinuation was similar for elacestrant vs. SOC (6 [5.2%] vs. 4 [3.8%]) with no individual event reported in ≥2% of patients.[98]

There were 4 on-study deaths in the patients with *ESR1-mut* (3 on elacestrant and 1 on SOC), but none of these were thought to be treatment-related. A similar proportion of serious TEAEs were reported across the two treatment arms (14 [12.2%] for elacestrant vs. 12 [11.3%] for SOC), none with an incidence ≥2%. None were deemed to be treatment-related in the SOC arm and only 2 (1.7%) in the elacestrant arm.[98]

Overall, elacestrant showed a predictable and manageable safety profile that is consistent with other ETs.[33] The safety profile in patients with *ESR1-mut* was consistent with the safety profile in All Patients.[98]

B.2.11 Ongoing studies

No ongoing studies of elacestrant are of relevance to this submission. The EMERALD trial is due to complete in August 2024, but no further data cuts are expected.

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principal findings from the clinical evidence base

EMERALD, a phase III, open-label, randomised study with 228 *ESR1-mut* positive patients (115 randomised to elacestrant and 113 to SOC endocrine monotherapy), demonstrates superiority of elacestrant regarding PFS in patients with ER+/HER2-, locally advanced or mBC with an activating *ESR1-mut* who had disease progression following at least one line of ET including a CDK4/6i.[33]

In EMERALD, treatment with elacestrant significantly reduced the risk of progression or death vs. SOC by 45% in patients with *ESR1-mut*, with PFS events per IRC occurring in 53.9% and 69% of patients respectively (HR: 0.55; 95% CI: 0.39 to 0.77, p-value=0.0005).[33,98] The Kaplan-Meier curves revealed an initial drop in both arms, highlighting possible primary endocrine resistance for some patients; however, subsequently there is clear separation of the curves, indicating a treatment benefit for patients who have ER-driven disease and maintain endocrine sensitivity.[33] Given the influence of the length of time on ET + CDK4/6i on subsequent treatment choice in ESMO guidelines,[12,77] this is an important consideration when considering data in this setting. EMERALD is the only trial of an oral SERD that mandated prior CDK4/6i use for all patients and allowed enrolment of patients with primary endocrine resistance.[33] The study therefore provided the opportunity to analyse prior ET+ CDK4/6i duration as a potential surrogate marker for endocrine sensitivity and elacestrant efficacy.

The analysis of patients with *ESR1-mut* with ≥12 months of prior ET + CDK4/6i, showed that the duration of prior ET + CDK4/6i in the metastatic setting was positively associated with PFS (the longer the duration on prior ET + CDK4/6i, the longer PFS on elacestrant vs. SOC). An absolute increase of 6.7 months in median PFS was observed with elacestrant (8.61 months; 95% CI 4.14 to 10.84) vs. SOC (1.91 months; 95% CI: 1.87 to 3.68). HR: 0.410; 95% CI: 0.262 to 0.634, p <0.0001.[28,30,100] The analysis in those patients with *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i (dual mutated) showed an absolute increase of 3.51 months in median PFS observed with elacestrant (5.45 months; 95% CI 2.14 to 10.84) vs. SOC (1.94 months; 95% CI: 1.84 to 3.94), with an HR of 0.423 (95% CI: 0.176 to 0.941).[28]

A similar drop in Kaplan-Meier curves was seen in the two *post hoc* subgroup analyses, although the drop was slightly reduced due to the selection of patients who remained endocrine sensitive. Since median PFS alone may not sufficiently interpret results in such a scenario, landmark analyses at 3, 6, 12, and 18 months were conducted. This analysis demonstrated the long and sustained clinical benefit of elacestrant vs. SOC in patients with *ESR1-mut*.[33] Of patients treated with elacestrant, 26.8% were free of progression at 12 months vs. 8.2% in the SOC arm, a 3-fold increment in the rates of patients alive and free of progression at 1 year for elacestrant-treated patients vs. patients treated with SOC.[33] Clinically significant PFS benefits for elacestrant vs. SOC, respectively, were also observed at 3 (55.93% vs. 39.55%), 6 (40.8% vs. 19.1%) and 18 months (24.33% vs. NA).[33,98] Landmark PFS analyses in the two *post hoc* subgroups, also favoured elacestrant at each

timepoint.[28,30,100,101] In the analysis in patients with *ESR1-mut* with ≥12 months of prior ET + CDK4/6i, of patients treated with elacestrant, 35.81% were free of disease progression at 12 months vs. 8.39% in the SOC group, a 4-fold increase in the rates of patients alive and free of progression at 1 year.[30,100]

In all patients with *ESR1-mut*, the findings of the PFS per IRC were reinforced by the analyses of secondary endpoints (including the key secondary endpoint OS), sensitivity analyses and pre-specified subgroup analyses, which numerically favoured the elacestrant arm.[98,99] Whilst OS results were not significant, they favoured elacestrant at the interim analysis of OS (HR 0.59; 95% CI: 0.36 to 0.96, p=0.0325)[33,98] and the final analysis of OS (HR 0.903; 95% CI: 0.629 to 1.298, p=0.5823),[102] as did estimates of OS at various timepoints, consistent with the PFS landmark analyses. Whilst no meaningful median OS advantage was seen with elacestrant vs. SOC in the subgroup of patients with *ESR1-mut* with ≥12 months of prior ET + CDK4/6i, analyses conducted at 3, 6, 12 and 18 months favoured the elacestrant group.[100] Meaningful median OS advantage was seen in the dual mutated subgroup and benefit was seen across multiple analysis points.[101]

QoL was maintained between treatment groups in the EMERALD trial and over time. EORTC QLQ-C30 scores were generally similar across treatment groups and time.[114] PRO-CTCAE results showed no clinically meaningful differences between treatment groups, and no noteworthy changes over time for change in patient-reported frequency, severity, or interference of symptoms from any TEAE. EQ-5D-5L scores were comparable across treatment arms with no notable differences over time and no meaningful change from baseline.[98,109] Results were similar in the two *post hoc* subgroup analyses.

During the treatment period for EMERALD, elacestrant showed a predictable and manageable safety profile that is consistent with other ETs.[33] AEs in both treatment arms were mainly Grade 1 and 2. The incidence of Grade 3 or 4 AEs was low in both treatment arms, with none exceeding 5%.[98] Among patients with *ESR1-mut*, there was a similar rate of TEAEs reported for elacestrant and SOC, irrespective of relationship to trial therapy (105 [91.3%] for elacestrant and 92 [86.8%] for SOC).[98] The most common TEAEs reported for both elacestrant and SOC were nausea (22.6% vs. 12.3%) and fatigue (12.2% vs. 11.3%).[98] There were very low incidences of dose reduction (6 [5.2%] vs. 0) and discontinuation (6 [5.2%] vs. 4 [3.8%]) for both elacestrant and SOC respectively.[98] There were 4 on-study deaths in the patients with *ESR1-mut* (3 on elacestrant and 1 on SOC), but none of these were thought to be treatment related.[98] A similar proportion of serious TEAEs were reported across the two treatment arms (14 [12.2%] for elacestrant vs. 12 [11.3%] for SOC), none with an incidence ≥2%.[98] None were deemed to be treatment related in the SOC arm and only 2 (1.7%) were deemed to be treatment related in the elacestrant arm.[98] Safety data for the two *post hoc* subgroups was consistent with those reported for All Patients and all patients with *ESR1-mut*.

In conclusion, elacestrant is the first oral SERD to demonstrate superiority over SOC endocrine monotherapy for PFS in patients with *ESR1-mut*, ER+/HER2-, locally advanced or mBC post ET + CDK4/6i.[33] Elacestrant showed a predictable and manageable safety profile that is consistent with other ETs.[33] In the sub-group of patients with *ESR1-mut*, ER+/HER2-, locally advanced or mBC who had received ≥12 months of prior ET + CDK4/6i, elacestrant continued to demonstrate superiority over SOC.[28,30,100]

B.2.12.2 Strengths and limitations of the clinical evidence base

B.2.12.2.1 Strengths of the evidence base

EMERALD was a randomised, phase III, controlled study in patients with ER+/HER2-, advanced or mBC, whose disease had progressed on 1 to 2 prior lines of ET, including a CDK4/6i. Treatment groups were well balanced with respect to all baseline disease and demographic characteristics.

EMERALD is generalisable to current UK clinical practice insofar as the inclusion criteria mandated the patients must have received a CDK4/6i prior to study entry, which is consistent with the current UK SOC in the advanced/metastatic setting and the treatments recommended by NICE in this setting. The trial enrolled patients in the UK (n=9 with an *ESR1-mut*).[98]

Although the *ESR1-mut*-positive patients in the EMERALD trial, on which this submission is based and elacestrant marketing authorisation is granted, comprise a subgroup of the full ITT population, *ESR1-mut* status was specified as one of the stratification factors and the trial was powered to detect significant improvements in PFS in this group of patients. The study required approximately 160 PFS events in this population to provide 80% power to detect an HR of 0.610 at the two-sided alpha level of 0.025,[33,98] however, the final PFS analysis was conducted after 140 events. The decision to modify the plan was based on a blinded PFS event projection analysis prior to unblinding that showed an additional year would have been needed to observe the pre-specified number of events.[98]

There was internal consistency amongst results in the EMERALD trial. The findings of the PFS analysis per IRC were reinforced by the analysis of secondary endpoints, including the key secondary endpoint OS (HR 0.59; 95% CI: 0.36 to 0.96, p=0.0325 in interim analysis[33,98] and HR 0.903; 95% CI: 0.629 to 1.298, p=0.5823 after final analysis)[102] Additionally, sensitivity analyses and HR estimates of PFS in pre-specified subgroups also supported the primary analysis.[98,99] Results from the two *post hoc* subgroup analyses also supported the primary efficacy analysis.

B.2.12.2.2 Potential limitations of the evidence base

Although the study was not blinded, efforts were made to minimise the risk of bias; the sponsor personnel performing statistical analyses were blinded to treatment assignments and aggregated data by treatment assignment until after the database lock. The study/sponsor team members were blinded to aggregated data by treatment assignment until after database lock and an independent central IRC, blinded to patients' treatment assignment, reviewed radiographic images and clinical information collected on-study to determine the endpoints of disease response and progression.[98,108]

In patients with *ESR1-mut* the Kaplan-Meier plot of PFS revealed an initial drop in both treatment arms. This is consistent with a recent study on fulvestrant in the same patient population.[112] There are two potential reasons for this observation. Firstly, this is likely to indicate possible primary endocrine resistance. Secondly, this may be due to the timing of the assessments i.e. the first assessment occurred at 8 weeks and there were a low number of early response assessments over the initial period of observation.

Finally, there are no targeted treatments indicated for *ESR1*-mutated advanced/mBC, therefore based on clinical feedback and the current reimbursed treatment pathway in England and Wales, the company position is that the appropriate comparators for this appraisal are everolimus in combination with exemestane (TA421),[19] and – for patients with both a *PIK3CA-mut* and *ESR1-mut* – alpelisib in combination with fulvestrant (per TA816).[20] Neither of these was the comparator in the EMERALD trial. As there is no direct comparative evidence available between elacestrant and the relevant comparators from the pivotal EMERALD study, an ITC was required to inform comparative efficacy in the cost-effectiveness model for this appraisal. The challenges associated with identifying and/or generating relevant evidence to support indirect comparison with UK-established clinical management in this setting are explored further in Section B.2.9.

B.2.12.3 Summary and conclusions

ER+/HER2- advanced/mBC is an incurable, devastating disease with poor treatment outcomes, which diminish with each line of therapy.[1–3] For those patients who do not require chemotherapy (which is used when there is a risk of imminent organ failure),[12] SOC treatment in the frontline advanced/metastatic setting is ET + CDK4/6i.[12] While 20% of patients progress rapidly on ET + CDK4/6i and are unlikely to benefit from further ET, many patients acquire resistance to ET + CDK4/6i over a longer time period.[13] Several molecular mechanisms have been identified that underlie the acquisition of ET resistance, including acquired mutations in *ESR1* (found in up to 50% of patients with ER+/HER2- advanced/mBC who progress on AI therapy).[14–16] These patients have faster disease progression and worse survival than those patients without an *ESR1-mut*.[17,18] Neither of the treatment regimens available for this population (everolimus + exemestane or alpelisib + fulvestrant) are specifically indicated for or tailored to the *ESR1* mutation.

Results from EMERALD show that elacestrant has the potential to meet a high unmet need for a tailored treatment for this novel population of patients with ER+/HER2- *ESR1*-mutated advanced/mBC who had disease progression after ≥12 months prior treatment with ET + CDK4/6i. The use of elacestrant delays disease progression and is well-tolerated and can be taken orally providing convenience for patients and caregivers.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A systematic literature review was conducted to identify published economic evaluations and cost-effectiveness studies of potential relevance to the decision problem addressed in this appraisal. Electronic database searches were originally conducted on 9th May 2021 ("2021 SLR"). The searches were updated first on 6th July 2022 ("2022 SLR") and subsequently on 29th April 2023 ("2023 SLR"), please see Appendix G for details.

In summary, no published cost-effectiveness studies of elacestrant were identified. Therefore, a *de novo* model was developed to inform this submission.

B.3.2 Economic analysis

A *de novo* economic model was constructed to assess the cost-effectiveness of elacestrant against alternative treatment options currently available in an NHS England setting, for the patient population relevant to this appraisal – people with ER+/HER2- advanced or mBC with *ESR1-mut*. No published economic evaluations considering elacestrant for the treatment of ER+/HER2- advanced/mBC were identified by the systematic literature review described in Section B.2.1.

B.3.2.1 Patient population

The population considered in the cost-effectiveness analysis is people with ER+/HER2- locally advanced or mBC with an activating *ESR1-mut* who have disease progression following ≥12 months prior treatment with ET + CDK4/6i. The *ESR1-mut* population is consistent with the marketing authorisation for elacestrant and the final scope issued by NICE. The restriction to people who were previously treated with ≥12 months of prior ET + CDK4/6i is based on feedback from clinicians in the UK to PFS data presented at the San Antonio Breast Cancer Symposium, of the place in therapy where elacestrant would be considered to provide most value in UK clinical pratice.[28–30]. The NICE final scope also identified a subpopulation of patients who also have a *PIK3CA-mut* (i.e., dual mutated), owing to the availability of a targeted therapy in the UK for patients with a *PIK3CA-mut*. As such, the cost-effectiveness model presents two populations:

1. *ESR1-mut* and ≥12 months of prior ET + CDK4/6i
2. *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i

Further details regarding the comparators relevant to this appraisal are presented in Section B.3.2.3.2.

Data concerning the safety and efficacy of elacestrant in the populations relevant to this appraisal are available from the EMERALD study. EMERALD was a phase III, international, multicentre, open-label, randomised controlled trial which enrolled postmenopausal women or men aged 18 years or older, with histologically or cytologically proven ER+/HER2-, advanced or mBC with disease progression following one to two prior lines of ET, which must have included a prior CDK4/6i. For further details concerning the EMERALD study, see Section B.2.3.1.

Data concerning the safety and efficacy of the comparators were sourced from the literature and Flatiron RWD. RWE for everolimus + exemestane and alpelisib + fulvestrant was sourced from Flatiron for the *ESR1-mut* who have received ≥12 months of prior ET + CDK4/6i and *ESR1-mut, PIK3CA-mut* who have received ≥12 months of prior ET + CDK4/6i

populations, respectively. To inform comparative efficacy, an MAIC was conducted on the elacestrant data from EMERALD to match to the Flatiron data available for the comparators. For further details concerning Flatiron and the ITC, see Section B.2.9.

B.3.2.2 Model structure

B.3.2.2.1 Model health states

A *de novo* cost-effectiveness model was developed in Microsoft Excel using an area-under-the-curve, partitioned survival analysis (PartSA) framework, where survival curves are used to determine health state occupancy. The model consists of three overarching health states: progression-free (or pre-progression), progressed disease (or post-progression) and death.

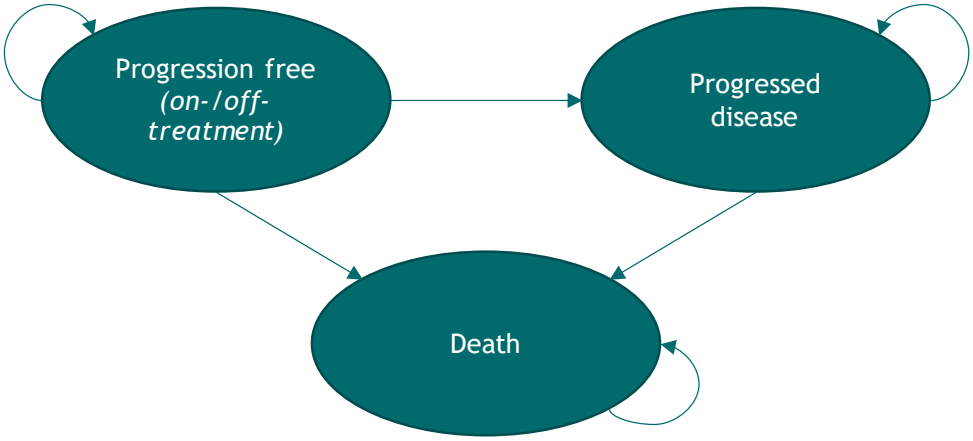
This structure was chosen for the following key reasons:

- A PartSA structure allows for an intuitive application of the outcome data captured in clinical trials of advanced or mBC patients and accurately reflects the progressive nature of advanced or mBC. This allows lifetime costs and health outcomes to be accurately estimated.
- Owing to the specification of survival curves to inform a PartSA structure, outputs from the ITC to compare elacestrant with everolimus in combination with exemestane, and alpelisib in combination with fulvestrant (in the dual mutated population), can be easily leveraged to generate comparisons.
- A PartSA structure, with the specification of progression-based health states, is consistent with previous NICE appraisals in ER+/HER2- advanced or mBC.[19,20]

The model schematic is presented in Figure 20. Patients enter the model in the progression-free health state where they receive treatment with elacestrant or a comparator. In each model cycle, patients can remain progression-free or transition to progressed disease or death. Once a patient progresses, they either remain in the progressed disease health state or transition to death in each model cycle. Death is an absorbing health state.

To accurately reflect cost and health outcomes, the progression-free health state is further divided into on- and off-treatment periods, as in practice patients may discontinue therapy prior to documented disease progression. In the model base case, it is assumed that patients discontinue active treatment with elacestrant upon progression, based on the licensed indication and standard clinical practice. In the SmPC, it is noted that treatment with elacestrant should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs.

Figure 20: Model schematic

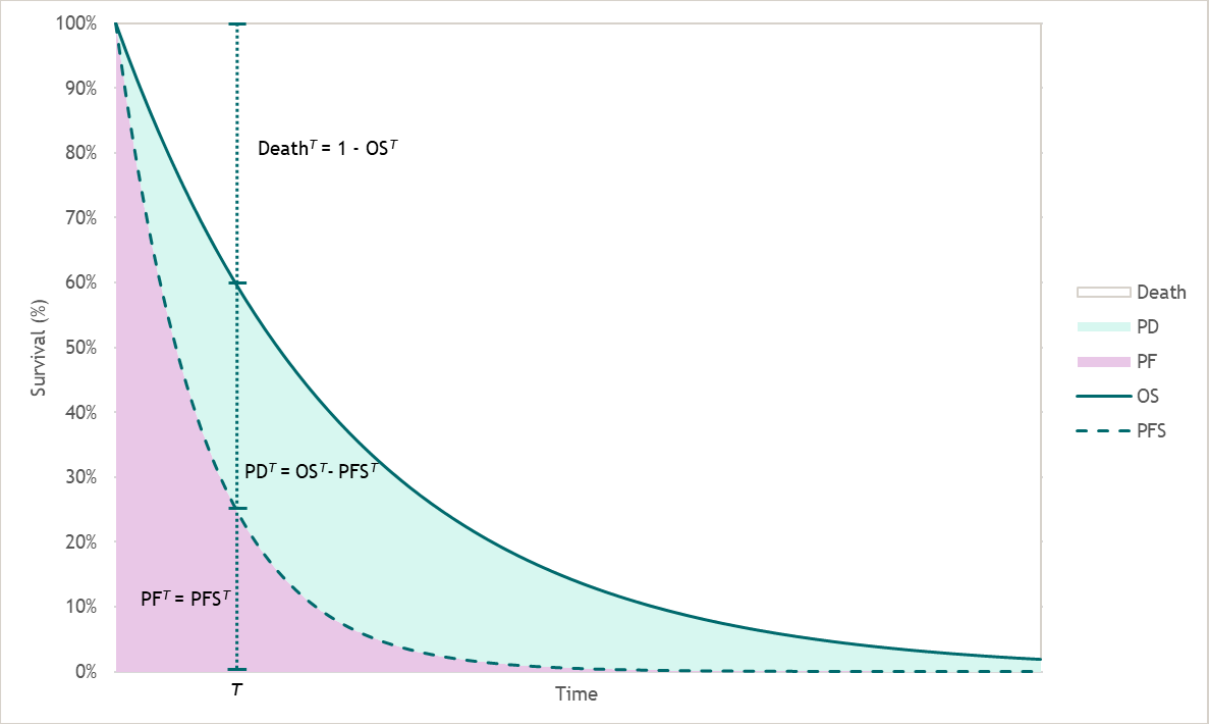


B.3.2.2.2 Health state occupancy

Health state occupancy is determined by independently modelled but non-mutually exclusive survival curves; namely, OS and PFS curves. Time to treatment discontinuation (TTD) curves are used to further partition the progression-free health state into on- and off-treatment periods.

Within a PartSA framework, the proportion of patients alive and free of progression at time *T* is equal to the PFS curve (PFS^T), the proportion of patients with progressed disease at time *T* is the difference between OS^T and PFS^T, and the proportion of patients in the death state is 1 minus OS^T. Figure 21 visually demonstrates how extrapolated parametric survival curves are used to derive health state occupancy within a PartSA model.

Figure 21: Health state occupancy, illustrative partitioned survival model



Abbreviations: OS, overall survival, PD, progressed disease; PF, progression free; PFS, progression-free survival.

Details of how the OS, PFS and TTD curves are derived are provided in Section B.3.4.

B.3.2.2.3 Model settings

As per the NICE reference case, all health effects were measured using quality-adjusted life years (QALYs), with a 3.5% discount applied to both costs and QALYs.[119] The analysis is conducted from the perspective of the NHS and Personal Social Services (PSS).

The NICE reference case stipulates that the time horizon of economic models should be long enough to reflect all important differences in costs or outcomes between technologies. As such, the cost-effectiveness analysis adopts a lifetime horizon of 37 years, which was considered long enough to adequately capture the lifetime of patients with advanced or mBC with a model entry age of approximately 63 years (note: model entry age differs by population), assuming no patients will survive beyond the age of 100 years (i.e., $100 - 63 = 37$).[33] Model entry age was based on baseline median age for elacestrant patients from EMERALD (see Table 39).

The model uses a 1-week cycle length, which is assumed to be short enough to adequately capture meaningful changes in health status for patients with advanced/mBC, being treated with elacestrant or a comparator. Due to the short cycle length, a half-cycle correction is not applied.

The most relevant previous NICE appraisal to this submission is for alpelisib in combination with fulvestrant for the treatment of advanced HR+/HER2-, *PIK3CA-mut* breast cancer (NICE TA816), though it should be noted that this population is not identical to the population relevant to this appraisal.[20] TA816 is most relevant when considering key issues throughout this appraisal, including (but not limited to) data availability for indirect comparison, inclusion of genomic testing costs, and the choice of appropriate utilities.

A summary of the main features of the economic analysis and the previous NICE appraisal are provided in Table 38.

Table 38: Features of the economic analysis

	Previous appraisal(s)	Current appraisal	
Factor	**TA816**[20]	**Chosen values**	**Justification**
Perspective	NHS and PSS	NHS and PSS	In line with the NICE reference case.
Model structure	Cohort level PartSA model	Cohort level PartSA model	Reflects the natural history of disease, allows for the incorporation of indirect treatment comparison, and is consistent with previous models.
Time horizon	Lifetime (40 years)	Lifetime (37 years)	Mean age of cohort upon model entry is approximately 63 years. A time horizon of 37 years was deemed sufficiently long to capture the full extent of both costs and effects. Alternative time horizons are explored in scenario analyses.
Cycle length	28-days (approximately monthly)	1 week (7 days)	A 7-day cycle length was considered short enough to adequately capture meaningful changes in the health status of patients with advanced/mBC.
Half-cycle correction	Yes	No	A half-cycle correction was not considered necessary due to the short cycle length.
Discount rate	3.5% for both costs and outcomes	3.5% for both costs and effects	In line with the NICE reference case. In the results provided, LYs are undiscounted for ease of interpretation (but can be discounted in the economic model submitted alongside this dossier).
Source of utilities	Utility values were estimated from EQ-5D-5L data from the SOLAR-1 trial (using the UK tariff), mapped onto the EQ-5D-3L[25]	Estimated from EQ-5D-5L data collected in the EMERALD study.	In line with the NICE reference case. Progressed utilities from Lloyd *et al*. (2006) are explored in scenario analyses. [76]
Source of costs	Resource use: NHS reference costs (2019/20) and NICE TA687/TA593 where applicable. [88, 136] Drug costs: BNF and eMIT.[120,121]	BNF, NHS National Cost Collection, eMIT, PSSRU, NIHR interactive costing tool. [120,121] [122,123]	In line with the NICE reference case.

Abbreviations: BNF, British National Formulary; eMIT, electronic market information tool; EQ-XD, Euro-QoL X-dimension; LY(s), life-year(s); mBC, metastatic Breast Cancer; NHS, National Health Service; NIHR, National Institute for Health Research; NICE, National Institute for Health and Care Excellence; PartSA, partitioned-survival analysis; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; TA, technology appraisal.

B.3.2.3 Intervention technology and comparators

B.3.2.3.1 Intervention

Elacestrant (KORSERDU®) is dosed at 345 mg orally once daily in the model, in line with the MHRA marketing authorisation.[27] It should be noted that in the EMERALD study, the dose of elacestrant is expressed as elacestrant dihydrochloride and is referred to as 400 mg in the study. Elacestrant is available as both 345 mg and 86 mg tablets, which are equivalent to 400 mg elacestrant dihydrochloride and 100 mg elacestrant dihydrochloride, respectively. Dose modification to 258 mg is permitted per the MHRA marketing authorisation in the presence of adverse reactions, though dose reductions are not captured in the model base-case analysis due to lacking data.[27] To account for the known dose intensity, the RDI of elacestrant from the EMERALD study was included in the model base-case. The exclusion of RDI is considered in scenario analysis.

B.3.2.3.2 Comparators

The final scope issued by NICE highlights four potential comparators to elacestrant:

- For patients with *ESR1-mut* breast cancer:
    - Everolimus + exemestane
    - Endocrine therapy with or without chemotherapy (ET+/-ChT)
    - Chemotherapy (ChT)
- For patients with *ESR1-mut* and *PIK3CA-mut* (dual mutated) breast cancer:
    - Alpelisib + fulvestrant

As described in Section B.1.3.4, treatment options for patients with ER+/HER2- *ESR1-mut* advanced/mBC who have disease progression following ≥12 months prior treatment with ET + CDK4/6i currently consist of everolimus + exemestane for patients without symptomatic visceral disease and alpelisib + fulvestrant (for patients with a *PIK3CA-mut*). The economic evaluation includes comparisons to everolimus + exemestane in the *ESR1-mut* population and alpelisib + fulvestrant in the dual mutated (*ESR1* and *PIK3CA*) population.

In the absence of treatments indicated in patients with *ESR1-mut* breast cancer, everolimus + exemestane is the most relevant comparator for elacestrant, and therefore represents the primary comparator in this submission. It should also be noted that the phase III study for everolimus + exemestane, BOLERO-2, did not include patients who progressed on treatment with CDK4/6 + ET which was indicated to be a prognostic factor by KOLs, thus the population is not comparable with EMERALD. Therefore, even though everolimus + exemestane is the most relevant comparator based on clinical current practice, there is no published evidence for everolimus + exemestane in an *ESR1-mut* population post CDK4/6i.

For patients with both *PIK3CA-mut* and *ESR1-mut*, alpelisib + fulvestrant is the most relevant comparator. This comparator is considered when the dual-mutated population is selected in the economic model. While data for alpelisib + fulvestrant from the SOLAR and BYLIEVE studies are published, the populations are not comparable to EMERALD. Only 20 patients (5.9%) in SOLAR had received prior treatment with a CDK4/6i, with no information regarding the amount of time patients were on treatment for. Similarly, no evidence is presented for an *ESR1-mut* population with ≥12 months prior treatment with a CDK4/6i in BYLIEVE. Additionally, no OS data are available from BYLIEVE for the *ESR1-mut* population. Therefore, despite alpelisib + fulvestrant being the most relevant comparator for Company evidence submission for elacestrant for oestrogen receptor-positive, HER2-negative advanced breast cancer with an *ESR1-mut* after at least 1 endocrine treatment

dual mutated patients based on clinical current practice, there is no published evidence for alpelisib + fulvestrant in an *ESR1-mut, PIK3CA-mut* population with ≥12 months prior treatment with a CDK4/6i.

ET+/-ChT is not included as a comparator in the economic evaluation – based on UK clinical expert opinion both of these treatments are rarely used in clinical practice in the population being considered in this submission and as such, these are not considered relevant comparators to elacestrant.[29] ChT is not included as a comparator in the economic evaluation as treatment with elacestrant is not expected to replace ChT in the treatment pathway. This is because, based on UK clinical expert opinion, treatment with chemotherapy is reserved for patients with imminent risk of organ failure, and thus is reserved for cases where aggressive treatment is required immediately.[12,29] In addition to this, ESMO treatment guidelines recommend sequential endocrine-based therapy before ChT, either in the absence of visceral crisis or until all endocrine-based options are exhausted.[77] However, ChT treatment is anticipated to be a treatment option for patients following discontinuation from elacestrant or everolimus + exemestane in the *ESR1-mut* population.

B.3.3 Clinical parameters and variables

B.3.3.1 ESR1-mut and ≥12 months of prior ET + CDK4/6i

Model efficacy estimates for elacestrant are presented based on the patient population with *ESR1-mut* who have received ≥12 months of prior ET + CDK4/6i in the EMERALD study.[33] Efficacy estimates for everolimus + exemestane are obtained from an MAIC analysis of patients with *ESR1-mut*, who received prior ET + CDK4/6i ≥12 months from the Flatiron RWD (see Section B.2.9).

B.3.3.2 Dual mutated and ≥12 months of prior ET + CDK4/6i

Model efficacy estimates for elacestrant are presented based on the *ESR1-mut*, *PIK3CA-mut* (dual mutated) patient population, who have received ≥12 months of prior ET + CDK4/6i in the EMERALD study. Efficacy estimates for alpelisib + fulvestrant are obtained from the MAIC analysis of patients with *ESR1-mut*, *PIK3CA-mut*, who received prior ET + CDK4/6i ≥12 months from the Flatiron RWD (see Section B.2.9).

B.3.3.3 Baseline patient characteristics

Baseline patient characteristics were based on the population in the EMERALD trial and are presented in Table 39. Mean age and the proportion of female patients were used in the economic model to calculate age- and sex-matched general population mortality rates and to estimate corresponding HRQoL. Body surface area (BSA) data from the trial was used to calculate drug acquisition costs for treatments with a BSA-based dosing regimen (discussed further in Section B.3.5.1.1).

Table 39: Baseline patient characteristics

Characteristic	Value		Source
	***ESR1-mut* and ≥12 months of prior ET + CDK4/6i**	**Dual mutated and ≥12 months of prior ET + CDK4/6i**	
Age (years)	[redacted]	[redacted]	EMERALD[33]
Proportion female	[redacted]	[redacted]	
BSA	[redacted]	[redacted]	

Abbreviations: BSA, body surface area; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy.

B.3.3.4 Efficacy

Efficacy data from the EMERALD study were used to inform OS, PFS and TTD within the economic model for elacestrant (*ESR1-mut* and ≥12 months of prior ET + CDK4/6i: n=78; dual mutated and ≥12 months of prior ET + CDK4/6i: n=27).[33] The EMERALD study is discussed in further detail in Section B.2.3.1. Efficacy for the comparators (everolimus + exemestane and alpelisib + fulvestrant) was based on relevant data from Flatiron, which is described in Section B.2.9.

To inform comparative efficacy of elacestrant versus the comparators, elacestrant data were matched to the data from the Flatiron dataset via an MAIC analysis, as described in Section B.2.9. More specifically:

- For population 1 *(ESR1-mut* and ≥12 months of prior ET + CDK4/6i): *ESR1-mut* and ≥12 months of prior ET + CDK4/6i elacestrant EMERALD data were matched to the everolimus + exemestane data from the Flatiron dataset
- Similarly for population 2 (dual mutated and ≥12 months of prior ET + CDK4/6i): dual mutated and ≥12 months of prior ET + CDK4/6i elacestrant EMERALD data were matched to the alpelisib + fulvestrant data from the Flatiron dataset.

Survival modelling was required to inform the economic model to estimate costs and QALYs over a lifetime horizon. Parametric survival models (PSMs) were fitted to the OS, PFS, and TTD data using the exponential, gamma, generalised gamma, Gompertz, log-logistic, log-normal, and Weibull distributions to inform the model. The most appropriate distribution was determined per guidance set out in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14.[124] The visual inspection of extrapolated survival, alongside Akaike and Bayesian information criteria (AIC, BIC) was used to determine the most appropriate model to characterise the Kaplan-Meier (KM) estimates of each endpoint. Clinical validation was sought to aid with the interpretation of OS and PFS estimates to assess the clinical plausibility of long-term outcomes and select an appropriate PSM to inform the base-case analysis. A description of the approach and rationale to inform the base case for each endpoint is discussed in turn throughout this section.

B.3.3.4.1 *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population

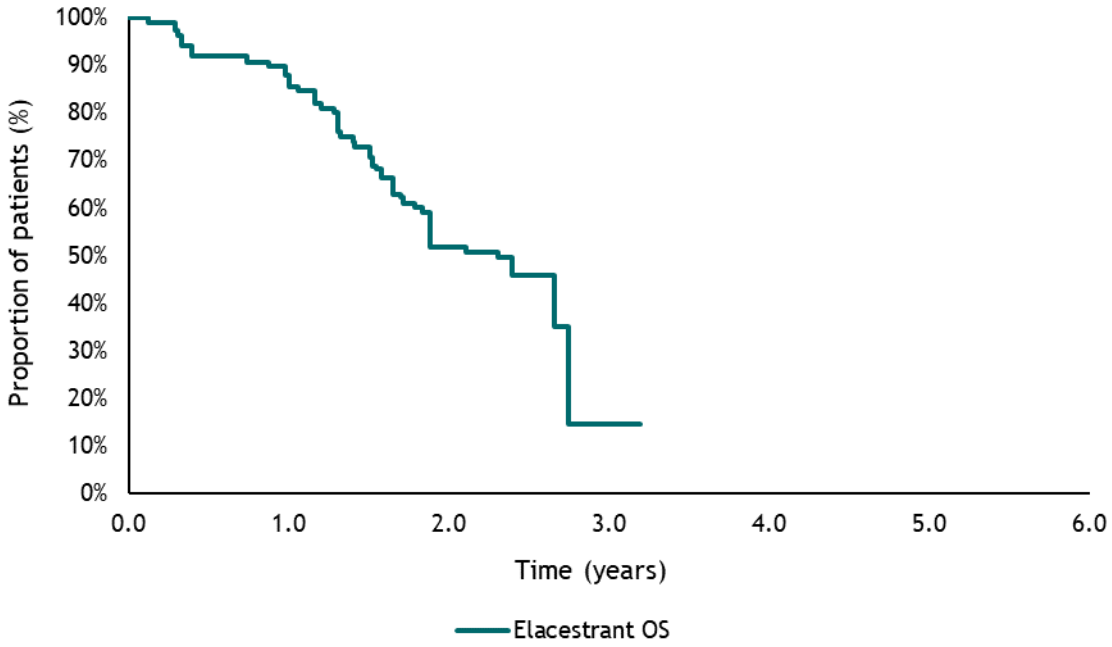
B.3.3.4.1.1 Elacestrant

Owing to the availability of patient-level data from the EMERALD study, independent curves were fitted to the weighted time-to-event outcomes; OS, PFS, and TTD. Throughout this section, data from EMERALD will be referred to as “elacestrant weighted to everolimus + exemestane”. The individual patient weights estimated from the MAIC analyses (matching elacestrant to everolimus + exemestane) are applied to the OS, PFS and TTD data from EMERALD to provide a comparison of outcomes. The weightings applied are estimated by the MAIC analyses aiming to achieve a balance between EMERALD and Flatiron based on prognostic factors and treatment effect modifiers (see Section B.2.9 for details).

Overall Survival

The KM estimate of OS for elacestrant from the EMERALD study for the *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population, weighted to everolimus + exemestane, is provided in Figure 22.

Figure 22: Kaplan-Meier plot | Elacestrant (weighted to everolimus + exemestane) OS | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population



Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; OS, overall survival.

AIC and BIC scores can be used to determine the relative fit of the PSMs to the observed data. The AIC and BIC for the elacestrant (weighted to everolimus + exemestane) OS PSMs are provided in Table 40. Based on the AIC and BIC scores, the Weibull model provided the best fit for elacestrant, though several other PSMs had relatively similar AIC/BIC fits. Figure 23 presents the parametric curve fits to the observed KM.

Table 40: Statistical goodness-of-fit scores | Elacestrant (weighted to everolimus + exemestane) OS | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population

Model	AIC	BIC	Rank	
			AIC	BIC
Exponential	342.10	344.45	7	7
Generalized gamma	334.16	341.23	5	5
Gompertz	332.93	337.64	2	2
Log-logistic	**334.04**	**338.75**	**4**	**4**
Log-normal	337.04	341.75	6	6
Weibull	332.50	337.21	1	1
Gamma	333.35	338.06	3	3

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; OS, overall survival.

Figure 23: Parametric curve fits | Elacestrant OS (weighted to everolimus + exemestane) | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; KM, Kaplan-Meier; OS, overall survival.

Each of the PSMs fit the data reasonably well between zero and approximately 2.5 years, except the exponential PSM which appears to underestimate OS. Owing to the large steps in the KM estimate towards the end of follow-up, the PSMs estimate a range of long-term survival predictions.

Table 41 presents the landmark OS estimates for elacestrant (weighted to everolimus + exemestane). The log-logistic and log-normal curves provide a good visual fit to the curve, prior to the drop in the tail, and predict reasonable estimates of OS in the long term. Clinical opinion described in Document B of TA816 (alpelisib submission) notes an expected 5% of patients alive with everolimus + exemestane treatment at 5 years.[20] Based on the separation observed in the KM curves until approximately 2.5 years (where the large steps occur towards the end of follow up), elacestrant is anticipated to show extended OS benefit over everolimus + exemestane, and thus greater than 5% of patients alive at 5 years. The base case extrapolation for everolimus + exemestane estimates 9% of patients alive at 5 years.

As such, extrapolations estimating greater than 9% of patients alive at 5 years for elacestrant were considered when selecting the base case curve.

Table 41: Landmark survival estimates | Elacestrant OS (weighted to everolimus + exemestane) | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population

Model	Landmark survival estimates (years)				
	1	2	3	5	10
Exponential	74.3%	54.8%	40.7%	22.5%	5.0%
Generalized gamma	83.8%	55.3%	26.8%	1.3%	0.0%
Gompertz	83.9%	56.6%	24.3%	0.1%	0.0%
Log-logistic	**83.5%**	**54.6%**	**34.5%**	**15.7%**	**4.3%**
Log-normal	80.5%	54.3%	37.4%	19.3%	5.4%
Weibull	83.8%	54.7%	29.6%	5.2%	0.0%
Gamma	82.8%	54.4%	32.4%	9.8%	0.3%

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; OS, overall survival.

Overall, the log-logistic PSM was considered appropriate to inform the base case assumptions, based on visual inspection of the PSM versus the KM estimate, and long-term survival projections. The statistical goodness-of-fit was also similar (within 5 points) of the statistically best fitting PSM (Weibull). Exploration of alternative curve fits is considered in scenario analysis.

Progression-free survival

The KM estimate of PFS for elacestrant (weighted to everolimus + exemestane) from the EMERALD study, for the *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population, is provided in Figure 24.

Figure 24: Kaplan-Meier plot | Elacestrant PFS (weighted to everolimus + exemestane) | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; PFS, progression-free survival.

The AIC and BIC for the elacestrant PFS (weighted to everolimus + exemestane) PSMs are provided in Table 42. Based on the AIC and BIC scores, the generalised gamma PSM provided the best statistical fit for elacestrant. Figure 25 presents the parametric curve fits to the KM estimates.

Table 42: Statistical goodness-of-fit scores | Elacestrant PFS (weighted to everolimus + exemestane) | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population

Model	AIC	BIC	Rank	
			AIC	BIC
Exponential	250.31	252.67	4	4
Generalized gamma	212.37	219.44	1	1
Gompertz	250.63	255.34	5	5
Log-logistic	245.92	250.64	3	3
Log-normal	**242.02**	**246.73**	**2**	**2**
Weibull	252.31	257.02	7	7
Gamma	252.13	256.84	6	6

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; PFS, progression-free survival.

Figure 25: Parametric curve fits | Elacestrant PFS (weighted to everolimus + exemestane) | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; KM, Kaplan-Meier; PFS, progression-free survival.

The generalised gamma model was the only model capable of reflecting an initial drop in PFS, followed by a levelling off, however this was considered to overestimate landmark survival estimates at 5 and 10 years providing higher estimates of PFS (8.3%) than OS (4.3%) at 10 years (see Section B.2.6.1). Table 43 presents the landmark survival estimates for elacestrant PFS (weighted to everolimus + exemestane).

Table 43: Landmark survival estimates | Elacestrant PFS (weighted to everolimus + exemestane) | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population

Model	Landmark survival estimates (years)				
	1	2	3	5	10
Exponential	37.0%	13.4%	5.0%	0.7%	0.0%
Generalized gamma	31.1%	20.7%	16.5%	12.3%	8.3%
Gompertz	36.2%	18.4%	11.9%	7.4%	5.4%
Log-logistic	30.8%	14.2%	8.6%	4.4%	1.7%
Log-normal	**32.2%**	**14.2%**	**7.8%**	**3.1%**	**0.7%**
Weibull	37.1%	13.6%	5.1%	0.7%	0.0%
Gamma	36.4%	12.3%	4.2%	0.5%	0.0%

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; PFS, progression-free survival.

Therefore, the log-normal PSM was considered appropriate to inform the base case assumptions based on long-term estimates and goodness-of-fit statistics. Exploration of the alternative curve fits are considered in scenario analysis.

Time to treatment discontinuation

Patient-level TTD data from the EMERALD study are used within the model to determine the drug and administration costs associated with elacestrant.

A summary of the TTD data for the elacestrant *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population (weighted to everolimus + exemestane) from EMERALD is provided as a KM estimate in Figure 26.

Figure 26: Kaplan-Meier plot | Elacestrant TTD (weighted to everolimus + exemestane) | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; TTD, time to treatment discontinuation.

As the TTD data from EMERALD are mature, TTD is informed by the KM curve directly in the base case in order to fully capture the costs associated with elacestrant treatment. Extrapolation with PSMs is explored in scenario analyses.

The AIC and BIC for the elacestrant TTD (weighted to everolimus + exemestane) PSMs are provided in Table 44. Based on the AIC and BIC scores, the generalised gamma model provided the best fit for elacestrant, with the log-normal providing a reasonably similar fit (within 10-points). Figure 27 presents the PSM fits to the KM estimate.

Table 44: Statistical goodness-of-fit scores | Elacestrant TTD (weighted to everolimus + exemestane) | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population

Model	AIC	BIC	Rank	
			AIC	BIC
Exponential	455.13	457.48	5	4
Generalized gamma	431.34	438.41	1	1
Gompertz	453.91	458.62	4	5
Log-logistic	442.37	447.08	3	3
Log-normal	438.63	443.34	2	2
Weibull	456.89	461.61	6	6
Gamma	457.03	461.74	7	7

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; TTD, time to treatment discontinuation.

Figure 27: Parametric curve fits | Elacestrant TTD (weighted to everolimus + exemestane) | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; KM, Kaplan-Meier; TTD, time to treatment discontinuation.

The PSMs fit the data reasonably well, though the exponential, Weibull and Gamma appear to slightly overestimate TTD between approximately 2 and 12 months. Table 45 presents the landmark TTD estimates for elacestrant.

Table 45: Landmark survival estimates | Elacestrant TTD (weighted to everolimus + exemestane) | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population

Model	Landmark survival estimates (years)				
	1	2	3	5	10
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; TTD, time to treatment discontinuation.

Overall, the KM curve for elacestrant TTD (weighted to everolimus + exemestane) is used to inform the base case. However, exploration of PSM curve fits are considered in scenario analysis.

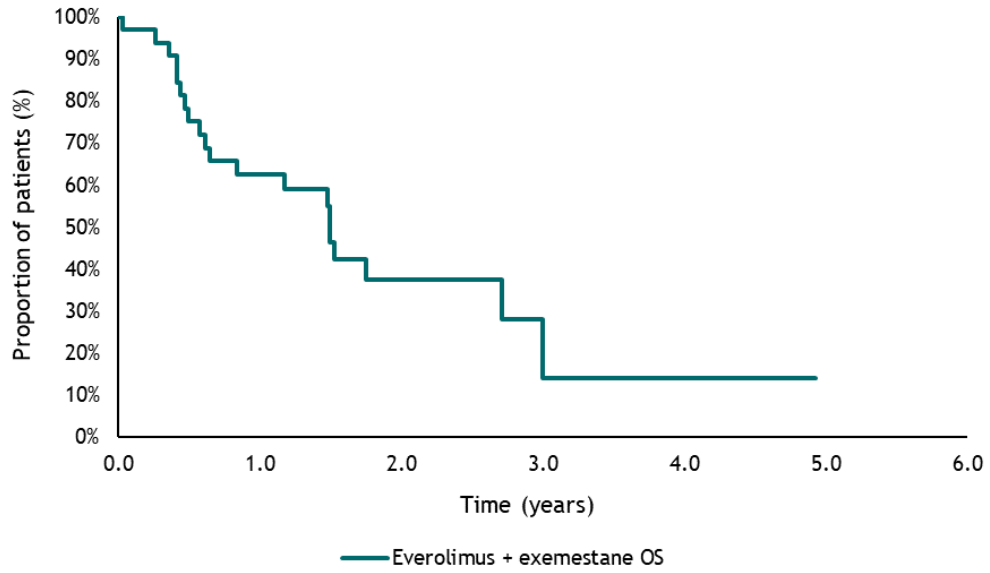
B.3.3.4.1.2 Everolimus + exemestane

To inform the efficacy of everolimus + exemestane, data was digitised from Flatiron, described in Section B.2.9. Pseudo patient-level data was then created using the Guyot algorithm.

Overall Survival

The KM estimate of OS for everolimus + exemestane from the Flatiron data is provided in Figure 28.

Figure 28: Kaplan-Meier plot | Everolimus + exemestane OS | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population



Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; OS, overall survival.

AIC and BIC scores can be used to determine the relative fit of the PSMs to the observed data. The AIC and BIC for the everolimus + exemestane OS PSMs are provided in Table 46. Based on the AIC and BIC scores, the exponential model provided the best fit for elacestrant, though several other PSMs had relatively similar AIC/BIC fits. Figure 29 presents the parametric curve fits to the observed KM.

Table 46: Statistical goodness-of-fit scores | Everolimus + exemestane OS | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population

Model	AIC	BIC	Rank	
			AIC	BIC
Exponential	173.17	174.63	1	1
Generalized gamma	176.57	180.97	7	7
Gompertz	175.10	178.03	5	5
Log-logistic	174.32	177.25	2	2
Log-normal	175.23	178.16	6	6
Weibull	175.10	178.03	4	4
Gamma	**175.01**	**177.94**	**3**	**3**

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; OS, overall survival.

Figure 29: Parametric curve fits | Everolimus + exemestane OS | *ESR1-mut* and ≥12 months of prior ET + *CDK4/6i* population

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; KM, Kaplan-Meier; OS, overall survival.

Each of the PSMs fit the data reasonably well between zero and approximately 3 years, with the log-logistic and log-normal curves predicting the greatest long-term OS for everolimus + exemestane.

Table 47 presents the landmark OS estimates for everolimus + exemestane. Clinicians estimated 5% of everolimus + exemestane patients would be alive at 5 years in the alpelisib submission (TA816).[20] However, all curves project survival greater than 5% at 5 years.

Table 47: Landmark survival estimates | Everolimus + exemestane OS | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population

Model	Landmark survival estimates (years)				
	1	2	3	5	10
Exponential	63.7%	40.3%	25.7%	10.4%	1.1%
Generalized gamma	63.4%	40.3%	27.0%	13.3%	3.1%
Gompertz	62.7%	40.2%	26.7%	12.7%	2.9%
Log-logistic	62.3%	38.6%	26.6%	15.3%	6.5%
Log-normal	61.2%	40.2%	29.0%	17.4%	7.1%
Weibull	64.6%	40.1%	24.7%	9.2%	0.7%
Gamma	**64.8%**	**39.8%**	**24.4%**	**9.0%**	**0.7%**

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; OS, overall survival.

Overall, the gamma PSM was considered appropriate to inform the base case assumptions, based on visual inspection of the PSM versus the KM estimate, goodness-of-fit statistics and long-term survival projections. Exploration of alternative curve fits is considered in scenario analysis.

Progression-free survival

The KM estimate of PFS for everolimus + exemestane from Flatiron for the *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population is provided in Figure 30.

Figure 30: Kaplan-Meier plot | Everolimus + exemestane PFS | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; PFS, progression-free survival.

The AIC and BIC for the everolimus + exemestane PFS PSMs are provided in Table 48. Based on the AIC and BIC scores, the log-logistic PSM provided the best statistical fit for everolimus + exemestane PFS. Figure 31 presents the parametric curve fits to the KM estimate.

Table 48: Statistical goodness-of-fit scores | Everolimus + exemestane PFS | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population

Model	AIC	BIC	Rank	
			AIC	BIC
Exponential	150.53	151.99	7	7
Generalized gamma	146.20	150.60	5	5
Gompertz	148.74	151.67	6	6
Log-logistic	144.20	147.14	1	1
Log-normal	**144.84**	**147.77**	**3**	**3**
Weibull	145.69	148.62	4	4
Gamma	144.62	147.55	2	2

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; PFS, progression-free survival.

Figure 31: Parametric curve fits | Everolimus + exemestane PFS | ESR1-*mut* and ≥12 months of prior ET + CDK4/6i population

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; KM, Kaplan-Meier; PFS, progression-free survival.

All PSMs provide a reasonable fit to the data, with the exponential underestimating PFS in the initial portion of the curve, and projecting greater PFS versus the other curve options at approximately 1 year.

Table 49 presents the landmark survival estimates for everolimus + exemestane PFS. All curves project relatively similar long-term estimates of PFS, with very few patients remaining progression-free at 2 years.

Table 49: Landmark survival estimates | Everolimus + exemestane PFS | ESR1-mut and ≥12 months of prior ET + CDK4/6i population

Model	Landmark survival estimates (years)				
	1	2	3	5	10
Exponential	12.5%	1.5%	0.2%	0.0%	0.0%
Generalized gamma	7.2%	0.4%	0.0%	0.0%	0.0%
Gompertz	5.9%	0.0%	0.0%	0.0%	0.0%
Log-logistic	8.4%	1.8%	0.7%	0.2%	0.0%
Log-normal	**9.0%**	**1.2%**	**0.3%**	**0.0%**	**0.0%**

Weibull	5.5%	0.0%	0.0%	0.0%	0.0%
Gamma	5.9%	0.1%	0.0%	0.0%	0.0%

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; PFS, progression-free survival.

Overall, the log-normal PSM was considered appropriate to inform the base case assumptions based on goodness-of-fit, visual fit and long-term estimates. Exploration of the alternative curve fits are considered in scenario analysis.

Time to treatment discontinuation

Two approaches for incorporating TTD for everolimus + exemestane in the model were explored:

1. Fit an exponential model to median duration of treatment sourced from the literature
2. Assume TTD is equal to PFS

For everolimus + exemestane, a median duration of 24 weeks was reported within the everolimus SmPC. [132] However, this was for a first-line population of patients with no *ESR1-mut*. Therefore, the estimate of treatment duration was considered to likely be too high to inform TTD in the model.

The second approach represents a scenario where patients would discontinue treatment upon disease progression, which is reflective of clinical practice. As there are no other available data to inform everolimus + exemestane TTD, the base case assumes TTD is equal to PFS.

B.3.3.4.2 ESR1-mut, PIK3CA-mut and ≥12 months of prior ET + CDK4/6i *population*

Throughout this section, data from EMERALD will be referred to as “elacestrant weighted to alpelisib + fulvestrant”. The individual patient weights estimated from the MAIC analyses (matching elacestrant to patients receiving alpelisib + fulvestrant) are applied to the OS, PFS and TTD data from EMERALD to provide a comparison of outcomes. The weightings applied are estimated by the MAIC analyses aiming to achieve a balance between EMERALD and Flatiron (see Section B.2.9 for details).

B.3.3.4.2.1 Elacestrant

The KM estimate of OS for elacestrant from the EMERALD study (weighted to alpelisib + fulvestrant), for the *ESR1-mut*, *PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population, is provided in Figure 32.

Figure 32: Kaplan-Meier plot | Elacestrant OS (weighted to alpelisib + fulvestrant) | *ESR1-mut*, *PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; OS, overall survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

The AIC and BIC for the elacestrant OS (weighted to alpelisib + fulvestrant) PSMs are provided in Table 50. Based on the AIC and BIC scores, the Gompertz model provided the best statistical fit to the KM data. However, this PSM gives unrealistic survival predictions at year 5 (i.e., no patients remain alive), meaning that the Weibull was instead selected to inform outcomes since this PSM provided both a good statistical fit and a realistic extrapolation of outcomes. Figure 33 presents the parametric curve fits to the observed KM.

Table 50: Statistical goodness-of-fit scores | Elacestrant OS (weighted to alpelisib + fulvestrant) | *ESR1-mut*, *PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population

Model	AIC	BIC	Rank	
			AIC	BIC
Exponential	90.62	91.92	7	5
Generalized gamma	89.88	93.77	6	7
Gompertz	88.00	90.59	1	1
Log-logistic	89.17	91.76	4	4
Log-normal	89.65	92.24	5	6
Weibull	**88.61**	**91.20**	**2**	**2**
Gamma	88.96	91.56	3	3

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; OS, overall survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Figure 33: Parametric curve fits | Elacestrant OS (weighted to alpelisib + fulvestrant) | *ESR1-mut*, *PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; KM, Kaplan-Meier; OS, overall survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

All curves provided a reasonable fit to the data aside from the exponential which underestimates survival until approximately 2 years. The generalized gamma model did not converge despite statistical adjustments being applied to the model to create a viable extrapolation. The landmark survival estimates for the elacestrant OS PSMs are provided in Table 51. From years 1 to 3, survival estimates are predicted to be similar by each model, At years 5 and 10, both the Gompertz and generalised gamma underestimate predicted survival by trying to capture the large drop in survival, which is likely an artifact of censoring.

Table 51: Landmark survival estimates | Elacestrant OS | *ESR1-mut*, *PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population

Model	Landmark survival estimates (years)				
	1	2	3	5	10
Exponential	83.2%	68.9%	57.3%	39.7%	15.7%
Generalized gamma	-	-	-	-	-
Gompertz	92.5%	73.4%	37.7%	0.0%	0.0%
Log-logistic	91.9%	70.9%	50.3%	24.9%	6.8%

Log-normal	90.4%	69.7%	52.5%	30.6%	9.9%
Weibull	**92.1%**	**71.0%**	**46.1%**	**11.4%**	**0.0%**
Gamma	91.4%	70.4%	49.1%	20.0%	1.3%

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; OS, overall survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Overall, the Weibull PSM was considered appropriate to inform the base-case based on visual fit to the KM curve, statistical goodness-of-fit and realistic long-term survival extrapolations. Exploration of alternative curve fits are considered in scenario analysis.

Progression-free survival

The KM estimate of PFS for elacestrant (weighted to alpelisib + fulvestrant) from the EMERALD study, for the *ESR1-mut*, *PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population, is provided in Figure 34.

Figure 34: Kaplan-Meier plot | Elacestrant PFS (weighted to alpelisib + fulvestrant) | *ESR1-mut*, *PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; PFS, progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

The AIC and BIC for the elacestrant PFS (weighted to alpelisib + fulvestrant) PSMs are provided in Table 52. Based on the AIC and BIC scores, the generalised gamma provides the best statistical fit to the KM data. Figure 35 presents the parametric curve fits to the observed KM.

Table 52: Statistical goodness-of-fit scores | Elacestrant PFS (weighted to alpelisib + fulvestrant) | *ESR1-mut*, *PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population

Model	AIC	BIC	Rank	
			AIC	BIC
Exponential	84.72	86.01	4	3
Generalized gamma	73.32	77.20	1	1
Gompertz	86.66	89.25	7	7
Log-logistic	84.16	86.75	3	4
Log-normal	**82.84**	**85.43**	**2**	**2**
Weibull	86.46	89.05	6	6
Gamma	86.06	88.65	5	5

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; PFS, progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Figure 35: Parametric curve fits | Elacestrant PFS (weighted to alpelisib + fulvestrant) | *ESR1-mut*, *PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; KM, Kaplan-Meier; PFS, progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

All curves show a reasonable fit to the data, aside from the generalized gamma, which underestimates the KM data until year 1 then overestimates after year 2. All models aside

from the generalized gamma, log-logistic and log-normal overestimate PFS at one year, with most models underestimating PFS in comparison to the KM data at 2 years.

Table 53 presents the landmark survival estimates for elacestrant PFS (weighted to alpelisib + fulvestrant). All curves predict similar PFS throughout, aside from generalized gamma, predicting a greater proportion of patients remaining progression-free at 5 years.

Table 53: Landmark survival estimates | Elacestrant PFS (weighted to alpelisib + fulvestrant) | *ESR1-mut*, *PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population

Model	Landmark survival estimates (years)				
	1	2	3	5	10
Exponential	30.7%	9.2%	2.8%	0.3%	0.0%
Generalized gamma	21.5%	12.4%	9.0%	6.1%	3.5%
Gompertz	30.6%	10.5%	4.2%	0.9%	0.1%
Log-logistic	23.0%	8.5%	4.6%	2.0%	0.7%
Log-normal	**24.3%**	**8.0%**	**3.5%**	**1.0%**	**0.1%**
Weibull	29.8%	7.2%	1.6%	0.1%	0.0%
Gamma	28.4%	6.2%	1.3%	0.1%	0.0%

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; PFS, progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Overall, the log-normal PSM was considered appropriate to inform the base-case based on visual fit to the KM curve, statistical goodness-of-fit and realistic long-term survival extrapolations. Exploration of alternative curve fits are considered in scenario analysis.

Time to treatment discontinuation

The KM estimate of TTD for elacestrant from the EMERALD study (weighted to alpelisib + fulvestrant), for the *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population, is provided in Figure 36.

Figure 36: Kaplan-Meier plot | Elacestrant TTD (weighted to alpelisib + fulvestrant) | *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TTD, time to treatment discontinuation.

Aligned with the comparison to everolimus + exemestane, elacestrant TTD (weighted to alpelisib + fulvestrant) is informed by the KM curve directly in the base case, to fully capture the costs associated with elacestrant treatment. Extrapolation with PSMs is explored in scenario analyses.

The AIC and BIC for the elacestrant TTD (weighted to alpelisib + fulvestrant) PSMs are provided in Table 54. Based on the AIC and BIC scores, the generalised gamma provides the best statistical fit to the data, though the log-logistic and log-normal models also provide reasonable statistical fits. Figure 37 presents the parametric curve fits to the observed KM.

Table 54: Statistical goodness-of-fit scores | Elacestrant TTD (weighted to alpelisib + fulvestrant) | *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population

Model	AIC	BIC	Rank	
			AIC	BIC
Exponential	121.56	122.78	5	4
Generalized gamma	108.23	111.89	1	1
Gompertz	120.73	123.17	4	5
Log-logistic	111.60	114.04	2	2
Log-normal	113.09	115.53	3	3
Weibull	123.32	125.76	6	6
Gamma	123.48	125.91	7	7

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TTD, time to treatment discontinuation.

Figure 37: Parametric curve fits | Elacestrant TTD (weighted to alpelisib + fulvestrant) | *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; KM, Kaplan-Meier; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TTD, time to treatment discontinuation.

All PSMs are observed to fluctuate between underestimating and overestimating the TTD for elacestrant (weighted to alpelisib + fulvestrant). Table 55 presents the landmark survival estimates for elacestrant TTD (weighted to alpelisib + fulvestrant).

Table 55: Landmark survival estimates | Elacestrant TTD (weighted to alpelisib + fulvestrant) | *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population

Model	Landmark survival estimates (years)				
	1	2	3	5	10
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Company evidence submission for elacestrant for oestrogen receptor-positive, HER2-negative advanced breast cancer with an *ESR1-mut* after at least 1 endocrine treatment

Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TTD, time to treatment discontinuation.

Overall, the KM curve for elacestrant TTD (weighted to alpelisib + fulvestrant) is used to inform the base case. However, exploration of PSM curve fits are considered in scenario analysis.

B.3.3.4.2.2 Alpelisib + fulvestrant

To inform the efficacy of alpelisib + fulvestrant, data was digitised from Flatiron, described in Section B.2.9. Pseudo patient-level data was then created using the Guyot algorithm.

Overall Survival

The KM estimate of OS for alpelisib + fulvestrant from the Flatiron data is provided in Figure 38.

Figure 38: Kaplan-Meier plot | Alpelisib + fulvestrant OS | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population

[redacted]

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; OS, overall survival.

PSMs were fit to the alpelisib + fulvestrant OS however, the generalised gamma model did not converge. AIC and BIC scores can be used to determine the relative fit of the PSMs to the observed data. The AIC and BIC for the alpelisib + fulvestrant OS PSMs are provided in Table 56. Based on the AIC and BIC scores, the gamma model provided the best fit for elacestrant, though all other PSMs had relatively similar AIC/BIC fits. Figure 39 presents the parametric curve fits to the observed KM.

Table 56: Statistical goodness-of-fit scores | Alpelisib + fulvestrant OS | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population

Model	AIC	BIC	Rank	
			AIC	BIC
Exponential	126.69	128.18	6	6
Generalized gamma	-	-	-	-
Gompertz	123.71	126.71	5	5
Log-logistic	122.44	125.43	4	4
Log-normal	122.33	125.32	2	2
Weibull	122.33	125.32	3	3
Gamma	**122.14**	**125.13**	**1**	**1**

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; OS, overall survival.

Figure 39: Parametric curve fits | Alpelisib + fulvestrant OS | *ESR1-mut* and ≥12 months of prior ET + *CDK4/6i* population

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; KM, Kaplan-Meier; OS, overall survival.

Each of the PSMs fit the data reasonably well between zero and approximately 3 years except the exponential and generalised gamma, with the log-logistic and log-normal curves predicting the greatest long-term OS for alpelisib + fulvestrant. Table 57 presents the

landmark OS estimates for alpelisib + fulvestrant. Only the Weibull and gamma represent feasible survival predictions where around 5% of patients are predicted to be alive at 5 years.[20]

Table 57: Landmark survival estimates | Alpelisib + fulvestrant OS | ESR1-mut and ≥12 months of prior ET + CDK4/6i population

Model	Landmark survival estimates (years)				
	1	2	3	5	10
Exponential	76.4%	58.1%	44.4%	26.0%	6.7%
Generalized gamma	-	-	-	-	-
Gompertz	85.3%	61.4%	31.8%	0.6%	0.0%
Log-logistic	86.1%	56.0%	34.0%	14.1%	3.3%
Log-normal	84.8%	55.3%	35.3%	15.4%	2.9%
Weibull	86.5%	58.3%	31.8%	5.2%	0.0%
Gamma	**86.1%**	**56.8%**	**32.7%**	**8.6%**	**0.2%**

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; OS, overall survival.

Overall, the gamma PSM was considered appropriate to inform the base case assumptions, based on visual inspection of the PSM versus the KM estimate, goodness-of-fit statistics and long-term survival projections. Exploration of alternative curve fits is considered in scenario analysis.

Progression-free survival

The KM estimate of PFS for alpelisib + fulvestrant from Flatiron for the *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population is provided in Figure 40.

Figure 40: Kaplan-Meier plot | Alpelisib + fulvestrant PFS | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; PFS, progression-free survival.

The AIC and BIC for the alpelisib + fulvestrant PFS PSMs are provided Table 58. Based on the AIC and BIC scores, the log-normal PSM provided the best statistical fit for alpelisib + fulvestrant PFS. Figure 41 presents the parametric curve fits to the KM estimate.

Table 58: Statistical goodness-of-fit scores | Alpelisib + fulvestrant PFS | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population

Model	AIC	BIC	Rank	
			AIC	BIC
Exponential	163.80	165.29	7	7
Generalized gamma	156.23	160.72	2	4
Gompertz	161.48	164.47	6	6
Log-logistic	156.73	159.72	4	3
Log-normal	**154.52**	**157.51**	**1**	**1**
Weibull	157.98	160.97	5	5
Gamma	156.42	159.41	3	2

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; PFS, progression-free survival.

Figure 41: Parametric curve fits | Alpelisib + fulvestrant PFS | ESR1-*mut* and ≥12 months of prior ET + *CDK4/6i* population

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; KM, Kaplan-Meier; PFS, progression-free survival.

All PSMs provide a reasonable fit to the data except the exponential model, which underestimates then overestimates PFS in the initial and tail portions of the curve. Table 59 presents the landmark survival estimates for alpelisib + fulvestrant PFS. All curves project relatively similar long-term estimates of PFS, with very few patients remaining progression-free at 3 years.

Table 59: Landmark survival estimates | Alpelisib + fulvestrant PFS | ESR1-mut and ≥12 months of prior ET + CDK4/6i population

Model	Landmark survival estimates (years)				
	1	2	3	5	10
Exponential	27.8%	7.6%	2.1%	0.2%	0.0%
Generalized gamma	21.2%	5.0%	1.9%	0.5%	0.1%
Gompertz	28.5%	1.4%	0.0%	0.0%	0.0%
Log-logistic	20.3%	4.6%	1.8%	0.5%	0.1%
Log-normal	**21.0%**	**3.5%**	**0.8%**	**0.1%**	**0.0%**
Weibull	24.9%	1.5%	0.0%	0.0%	0.0%
Gamma	22.7%	1.8%	0.1%	0.0%	0.0%

Abbreviations**:** CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; PFS, progression-free survival.

Overall, the log-normal PSM was considered appropriate to inform the base case assumptions based on goodness-of-fit, visual fit and long-term estimates. Exploration of the alternative curve fits are considered in scenario analysis.

Time to treatment discontinuation

Per the comparison to everolimus + exemestane, the base case assumes TTD is equal to PFS for alpelisib + fulvestrant. This is reflective of a scenario where patients would discontinue treatment upon disease progression, which is reflective of clinical practice.

B.3.3.4.3 Summary of base-case PSM curve fit selection

A summary of the PSMs used to inform the base-case analysis for both populations is provided in Table 60.

Table 60: Summary of base-case PSM curve fits

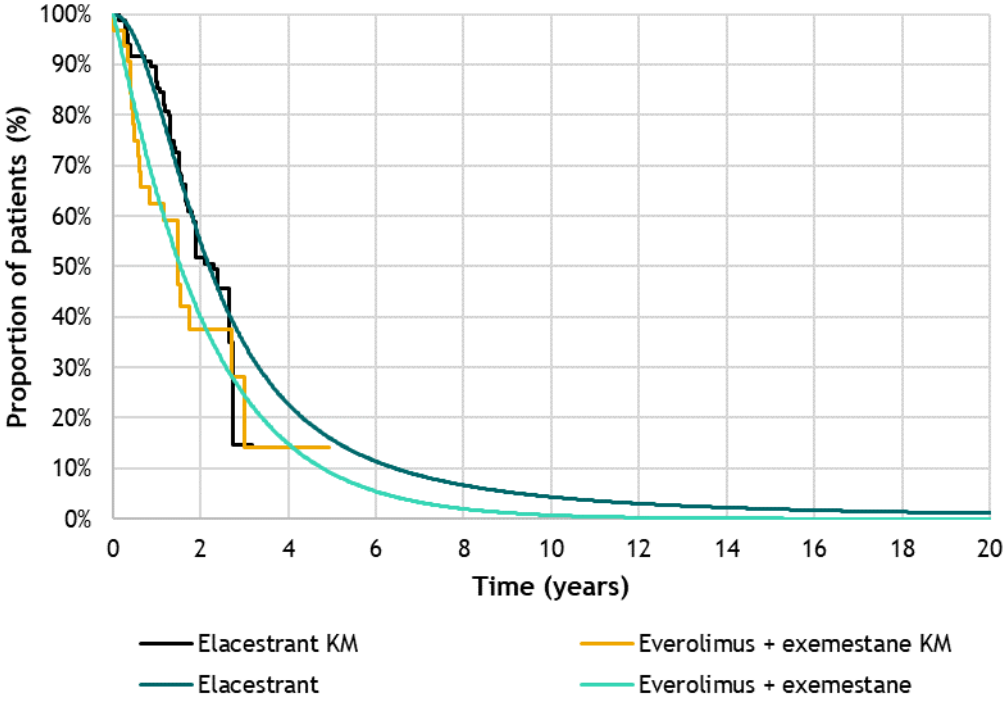
Population	Treatment	Outcome	Choice of PSM
ESR1-mut and ≥12 months of prior ET + CDK4/6i	Elacestrant	OS	Log-logistic
		PFS	Log-normal
		TTD	KM curve
	Everolimus + exemestane	OS	Gamma
		PFS	Log-normal
ESR1-mut, PIK3CA-mut and ≥12 months of prior ET + CDK4/6i	Elacestrant	OS	Weibull
		PFS	Log-normal
		TTD	KM curve
	Alpelisib + fulvestrant	OS	Gamma
		PFS	Log-normal

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PSM parametric survival model; TTD, time to treatment discontinuation.

B.3.3.4.3.1 OS summary

A summary of the base case OS estimates for elacestrant versus everolimus + exemestane and alpelisib + fulvestrant are presented in Figure 42 and Figure 43, respectively.

Figure 42: *ESR1-mut* and ≥12 months of prior ET + CDK4/6i | OS base case summary



Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; KM, Kaplan-Meier; OS, overall survival.

Note: Curves are adjusted for background mortality. Elacestrant data is weighted to everolimus + exemestane.

Figure 43: *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i | OS base case summary

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; KM, Kaplan-Meier; OS, overall survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.
Note: Curves are adjusted for background mortality. Elacestrant data is weighted to alpelisib + fulvestrant.

B.3.3.4.3.2 PFS summary

A summary of the base case PFS efficacy for elacestrant versus everolimus + exemestane and alpelisib + fulvestrant are presented in Figure 44 and Figure 45, respectively.

Figure 44: *ESR1-mut* and ≥12 months of prior ET + CDK4/6i | PFS base case summary

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; KM, Kaplan-Meier; PFS, progression-free survival.

Note: Curves are adjusted for background mortality and OS. Elacestrant data is weighted to everolimus + exemestane.

Figure 45: *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i | PFS base case summary

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; KM, Kaplan-Meier; PFS, progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.
Note: Curves are adjusted for background mortality and OS. Elacestrant data is weighted to alpelisib + fulvestrant.

B.3.3.4.3.3 TTD summary

A summary of the base case TTD efficacy for elacestrant versus everolimus + exemestane and alpelisib + fulvestrant are presented in Figure 46 and Figure 47, respectively.

Figure 46: *ESR1-mut* and ≥12 months of prior ET + CDK4/6i | TTD base case summary

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; KM, Kaplan-Meier; TTD, time to treatment discontinuation.
Note: Curves are adjusted for background mortality and OS. Elacestrant data is weighted to everolimus + exemestane.

Figure 47: *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i | TTD base case summary

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; KM, Kaplan-Meier; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TTD, time to treatment discontinuation.
Note: Curves are adjusted for background mortality and OS. Elacestrant data is weighted to alpelisib + fulvestrant.

B.3.4 Efficacy measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

In the EMERALD study, HRQoL outcomes were assessed using multiple disease specific and generic instruments, including the EQ-5D-5L. EQ-5D-5L questionnaires were completed by patients on days 1 and 15 of cycle, day 1 of cycles 1-4, day 1 of every other cycle between cycles 6-34, at the EOT, at post-treatment safety follow-up and on unscheduled visits. For this analysis, data from unscheduled visits were excluded from the dataset.

B.3.4.2 Mapping

EQ-5D-5L data were collected in the EMERALD trial, however, NICE does not recommend using the EQ-5D-5L values set for technology appraisals.[119] The NICE reference case recommends mapping EQ-5D-5L data to EQ-5D-3L using the function developed by the NICE DSU (Hernández-Alava *et al.* [2017]).[125] The following health states were considered for the health-state utility values:

- Baseline (before treatment initiation)
- Pre-progression

- Post-progression

In addition, baseline age, number of prior lines of therapy and grade 3+ AEs were considered. HRQoL is not expected to differ between treatment arms, though if any differences were present, these are expected to be captured by the grade 3+ AE term.

Baseline utility, baseline age and number of prior lines of therapy were collected at cycle 1, day 1. The AE variable was defined by whether an individual had a grade 3+ AE ongoing at the time of the EQ-5D assessment. The progression status variable was determined by whether an individual had progressed disease at the time of EQ-5D assessment.

Data from the *ESR1-mut* population of EMERALD were used to inform the economic model for both model populations, to allow for a greater number of observations to be included in the analysis. The number of observations and descriptive utility statistics by health state are presented in Table 61.

Table 61: Descriptive utility statistics by health state

Health state	Observation	Mean (SD)	Median
Progression-free	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]

Abbreviations: SD, standard deviation.

The mapped EQ-5D-3L utility values were analysed using a linear mixed-effects regression model, with patient ID included as a random-effect term and the prognostic factors (baseline utility, baseline age, number of prior lines of therapy, grade 3+ AE, progression status) included as fixed-effects. This model allows for the consideration of repeated EQ-5D-3L measurements at the patient level, given each individual may provide several assessments during the study follow-up period. All prognostic factors were included in the base case model, with all except the 'number of prior lines of treatment' found to be statistically significant at the 0.05 level.

A summary of the predicted utility values (derived from the statistical regression model) by health state used in the economic model are presented in Table 62.

Table 62: Predicted utility values by health state

Health state	Mean	SE	95% CI
Progression-free	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; SE, standard error.

B.3.4.3 Health-related quality-of-life studies

Please see Appendix H for details.

B.3.4.4 Adverse reactions

AEs considered in the model were grade ≥3 AEs with an incidence of ≥2% for elacestrant or the comparators of interest. AE occurrence was sourced from the *ESR1-mut* population of EMERALD for elacestrant and the literature for everolimus + exemestane and alpelisib + fulvestrant.[22,25] AE frequency is presented in Table 63.

Table 63: Grade 3+ AE frequency occurring in ≥2% of patients

AE	Elacestrant	Everolimus + exemestane	Alpelisib + fulvestrant
Anaemia	1.7%	6.0%	0.0%
ALT increase	0.9%	3.0%	0.0%
AST increase	1.7%	3.0%	0.0%
Asthenia	2.6%	2.0%	1.8%
Back pain	4.3%	0.0%	0.0%
Bone pain	2.6%	0.0%	0.0%
Diarrhoea	0.0%	2.0%	6.7%
Dyspnoea	0.0%	4.0%	0.0%
Fatigue	1.7%	3.0%	3.5%
Hyperglycaemia	0.0%	4.0%	36.6%
Mucosal inflammation	0.0%	0.0%	2.1%
Nausea	4.3%	0.0%	2.5%
Pneumonitis	0.9%	3.0%	0.0%
Rash	0.9%	1.0%	9.9%
Stomatitis	0.0%	8.0%	2.5%
Thrombocytopenia	0.0%	3.0%	0.0%
Vomiting	1.7%	0.0%	0.7%

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, Aspartate aminotransferase.

As the utility regression included a term for grade 3+ AEs ongoing at the time of the EQ-5D assessment, the impact of AEs on HRQoL were considered to be accounted for sufficiently within the health state utility estimates. This approach is considered to avoid double counting and is aligned with the NICE appraisal for alpelisib (TA816).

Inclusion of AE disutilities were explored in scenario analyses to account for differences in toxicity profiles between elacestrant, everolimus + exemestane and alpelisib + fulvestrant. In the scenario, disutilities were applied as a one-off QALY decrement per treatment arm by calculating the sum product of all AE disutilities and their respective durations. For all events, disutilities and durations were assumed to take mean values as sourced from literature, presented in Table 64.

Table 64: Disutilities for captured adverse events

AE	Disutility	Duration (days)	Source: Disutility	Source: Duration
Anaemia	-0.119	7	Swinburn et al. (2010)[126]	Assumed 1 model cycle
ALT increase	-0.050	28	Telford *et al*. (2019)[127]	Telford *et al*. (2019)[127]
AST increase	-0.050	28	Assumed equal to ALT increase	Assumed equal to ALT increase
Asthenia	-0.115	27	Assumed equal to fatigue	Assumed same as fatigue
Back pain	-0.069	17	Telford *et al*. (2019) [127]	Telford *et al*. (2019)[127]

Bone pain	-0.069	17	Telford *et al*. (2019) [127]	Telford *et al*. (2019) [127]
Diarrhoea	-0.103	21	Lloyd *et al*. (2006)[76]	Hagiwara *et al*. (2017)[128]
Dyspnoea	-0.050	12.7	Telford *et al*. (2019) [127]	Telford *et al*. (2019) [127]
Fatigue	-0.115	27	Lloyd *et al*. (2006)[76]	Hagiwara *et al*. (2017)[128]
Hyperglycaemia	-0.081	7	Smith-Palmer *et al*. (2016)[129]	Assumed 1 model cycle
Mucosal inflammation	-0.008	25	Assumed equal to pneumonitis	Hagiwara *et al*. (2017)[128]
Nausea	-0.021	7	Mistry *et al*. (2018)[130]	Assumed 1 model cycle
Pneumonitis	-0.008	25	Marti *et al*. (2013)[131]	Assumed equal to mucosal inflammation
Rash	-0.030	21	Paracha *et al*. (2018)[132]	Hagiwara *et al*. (2017)[128]
Stomatitis	-0.151	25	Lloyd *et al*. (2006)[76]	Assumed equal to mucosal inflammation
Thrombocytopenia	-0.108	7	Tolley *et al*. (2013)[133]	Assumed equal to anaemia
Vomiting	-0.103	28	Lloyd *et al*. (2006)[76]	Hagiwara *et al*. (2017)[128]

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, Aspartate aminotransferase.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Analysis of the EQ-5D data collected in the EMERALD study were used to inform the utility value for the progression-free and progressed disease health states (as described in Sections B.3.4.1 and B.3.4.2).[33] Alternative values sourced from the literature and previous NICE technology appraisals were explored in scenario analyses (presented in the cost-effectiveness model, Table 85 and Table 86).

An adjustment for age-related utility decrements was included in the model to account for the natural age-related decline in quality of life. This adjustment was applied by estimating general population utility values at each age using the Ara & Brazier (2010) algorithm, to determine a utility multiplier linked to the starting age of the modelled cohort.[135] The formula used to estimate general population utility (which then informs the multiplier) is shown below:

$$General\ population\ utility\ value = 0.9508566 + 0.0212126 \times male - 0.0002587 \times age - 0.0000332 \times age^2$$

A summary of utility inputs for the cost-effectiveness model is presented in Table 65.

Table 65: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Progression-free	[redacted]	([redacted], [redacted])	Section B.3.4.2, Page 142	EQ-5D-5L data mapped to EQ-5D-3L as derived from the relevant patient population
Post-progression	[redacted]	([redacted], [redacted])	Section B.3.4.2, Page 142	

Abbreviations: EQ-XD, Euro-QoL X-dimension.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Drug acquisition costs

The unit drug costs for each treatment included within the cost-effectiveness model and its source are summarised in Table 66. The unit costs are sourced from the British National Formulary (BNF) and the drugs and pharmaceutical electronic market information tool (eMIT).[120,121] The proposed NHS list prices for elacestrant are [redacted] and [redacted] for the 345mg and 86mg packs. A proposed Patient Access Scheme (PAS) for elacestrant at fixed prices of [redacted] (345mg) and [redacted] (86mg) per 28-tablet pack is incorporated throughout the results section (Section B.3.9).

The lowest cost of everolimus for each dosage was taken from the BNF, reflecting a small reduction in its cost versus its branded variant (Afinitor®, Novartis), as generic everolimus has only been available since October 2023, a stable price is not yet available.[135] Both exemestane and fulvestrant have been made available as generic medicines for several years, and so these costs were taken from eMIT.[121]

Table 66: Unit drug costs

Treatment	Units (mg)	Pack size	Pack cost (£)	Source
Elacestrant (proposed list)	345	28	[redacted]	Menarini Stemline
	86		[redacted]	
Elacestrant (PAS)	345		[redacted]	
	86		[redacted]	
Everolimus	2.5	30	£1,020.00	BNF – (2024) *Sandoz Ltd*[135]
	5		£1,912.50	
	10		£2,272.05	
Exemestane	25	30	£4.25	eMIT (2023)[121]
Alpelisib	150	56	£4,082.14	BNF – Alpelisib (2023)[136]
	200	28	£4,082.14	
Fulvestrant	250	2	£80.18	eMIT (2023)[121]

Abbreviations: BNF, British National Formulary; eMIT, electronic market information tool; PAS, patient access scheme.

Dosing

The dosing schedule for all treatments was taken from the relevant SmPC.

Elacestrant is administered orally at a dose of 345 mg daily, and treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.[27]

Everolimus + exemestane is administered orally at a dose of 10 mg everolimus and 25 mg exemestane daily. Everolimus is administered until no clinical benefit is observed or until unacceptable toxicity occurs. Exemestane is administered until tumour progression is evident.[137,138]

In the alpelisib + fulvestrant regimen, alpelisib is administered orally at a dose of 300 mg daily. 500 mg of fulvestrant is administered via intramuscular (IM) injection on days 1, 15 and 29, and once monthly thereafter. Treatment with alpelisib + fulvestrant should continue until no clinical benefit is observed, or until unacceptable toxicity occurs.[93]

RDI

RDI is included in the model for elacestrant and the comparators to account for dose interruptions and modifications. Table 67 presents the RDI values incorporated in the economic model. An exploratory analysis where RDI is excluded is presented in scenario analyses.

Table 67: Relative dose intensity estimates

Regimen	Treatment	RDI	Source
Elacestrant	Elacestrant	[redacted]	EMERALD *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population
Everolimus + exemestane	Everolimus	98.0%	Jerusalem *et al*. (2016)[139]
	Exemestane	100.0%	
Alpelisib + fulvestrant	Alpelisib	94.0%	Alaklabi *et al*. (2022)[140]
	Fulvestrant		

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; RDI, relative dose intensity.

B.3.5.1.2 Treatment administration costs

The unit administration cost for treatments given by IM injection (i.e., the fulvestrant component of alpelisib + fulvestrant) is represented by the cost of 10 minutes of a general practice nurse's time, sourced from the Personal Social Services Research Unit (PSSRU). A cost of £8.67 is applied for each administration of fulvestrant within the alpelisib + fulvestrant regimen. As all other treatments are administered orally, it is assumed that no administration costs are incurred.

B.3.5.2 Health-state unit costs and resource use

Table 68 presents the resource use frequencies associated with the progression-free and progressed disease health states. Resource use comprised general practitioner (GP) visit, oncology specialist visit, community nurse visit, clinical nurse specialist, social worker, physiotherapist, computed tomography (CT) scan and lymphoedema nurse. The resources and monthly frequency of resource use were sourced from the NICE technology appraisal of

palbociclib for HR+, HER2- advanced/mBC (TA619).[141] Frequencies were converted from monthly to 7-day frequencies to align with the model cycle length.

Table 68: Healthcare resource use estimates

Resource	Frequency (per month)		Source
	Progression-free	Post-progression	
GP visit	1.00	1.50	NICE TA619: Committee papers[141]
Oncology specialist visit	0.17	0.50	
Community nurse	0.33	0.67	
Clinical nurse specialist	1.00	2.00	
Social worker	0.50	0.50	
Physiotherapist	0.00	0.50	
CT scan	0.33	0.33	
Lymphoedema nurse	0.00	0.50	

Abbreviations: CT, computerized tomography; GP, general practitioner; NICE, National Institute for Health and Care Excellence; TA, technology appraisal.

Table 69 presents unit costs for healthcare resource use items, which were sourced from the NHS National Cost Collection (2021/22) and PSSRU.[122,123] The resulting healthcare resource use costs per 7-day model cycle were £51.80 and £100.78 in the progression-free and progressed disease health states, respectively.

Table 69: Healthcare resource use unit costs

Resource	Unit cost	Source
GP visit	£41.00	PSSRU (2022)[123]
Oncology specialist visit	£188.57	NHS Cost Collection (2021/22)[122]
Community nurse	£52.00	PSSRU (2022)[123]
Clinical nurse specialist	£63.00	PSSRU (2022)[123]
Social worker	£50.00	PSSRU (2022)[123]
Physiotherapist	£48.50	PSSRU (2022)[123]
CT scan	£142.47	NHS Cost Collection (2021/22)[122]
Lymphoedema nurse	£53.00	PSSRU (2022)[123]

Abbreviations: CT, computerized tomography; GP, general practitioner; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

B.3.5.3 Adverse reaction unit costs and resource use

The unit costs associated with managing the grade ≥3 AEs which occur in ≥2% of patients (as described in Section B.3.4.4) were sourced from the NHS Cost Collection.[122] The costs associated with each AE are shown in Table 70.

Table 70: Unit costs per adverse events captured in the model

Adverse event	Cost of event	Source
Anaemia	£2,015.26	NHS Cost Collection 2021/22[122]
ALT increase	£2,214.32	
AST increase	£2,214.32	
Asthenia	£2,015.26	

Back pain	£1,186.77	
Bone pain	£1,273.43	
Diarrhoea	£1,746.82	
Dyspnoea	£862.68	
Fatigue	£2,015.26	
Hyperglycaemia	£1,365.50	
Mucosal inflammation	£1,746.82	
Nausea	£1,746.82	
Pneumonitis	£862.68	
Rash	£1,902.34	
Stomatitis	£1,746.82	
Thrombocytopenia	£993.37	
Vomiting	£1,746.82	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; NHS, National Health Service.

The unit costs for each AE were multiplied by the respective frequency of the AE for each treatment (Table 63) and applied as a one-off upfront cost to each treatment arm included in the model. The total costs of adverse events by treatment arm are presented in Table 71.

Table 71: Unit costs per adverse events

Treatment	Total adverse event costs
Elacestrant	£395.62
Everolimus + exemestane	£706.60
Alpelisib + fulvestrant	£920.83

B.3.5.4 Miscellaneous unit costs and resource use

B.3.5.4.1 *ESR1-mut* testing

The NHS does not currently fund genomic testing for *ESR1-mut* since elacestrant is the first available therapy for patients with ER+/HER2- *ESR1-mut* advanced/mBC. Future funding is expected, in line with genomic testing for *PIK3CA-mut*. At the time of the appraisal of alpelisib + fulvestrant for treating ER+/HER2-, *PIK3CA-mut* advanced/mBC (TA816), *PIK3CA-mut* were not routinely funded. The genomic test for *PIK3CA-mut* is now included in the latest National Genomic Test Directory for Cancer (solid tumours; code M3.6). As identifying an *ESR1* mutation will be required for treatment with elacestrant, the ability to account for the financial impact of implementing the genomic test is included in the economic model.

The cost of testing is calculated using the expected cost of £300 based on digital polymerase chain reaction (dPCR) testing, multiplied by the proportion of tested patients who have the *ESR1-mut* in a prevalence-based approach. The base-case analysis assumes that *ESR1-mut* are found in up to 50% of patients with ER+/HER2- advanced/mBC who progress on AI therapy.[15,16] The approaches used to account for genomic testing (and total costs) are shown in Table 72.

Table 72: *ESR1-mut* testing cost approaches

Mutation testing approach	Total *ESR1-mut* testing cost	Source
Cost taken directly from the NIHR interactive costing tool	£300.00	Based on dPCR testing
Prevalence based costing approach (base case) (£300 × 1 / proportion of patients with *ESR1-mut*)	£857.46	Jhaveri *et al*., Lin *et al*. [15,16]

Abbreviations: dPCR, digital polymerase chain reaction; *ESR1*, oestrogen receptor 1 gene; NIHR, National Institute for Health and Care Research.

ESR1-mut testing costs are applied to the elacestrant arm of the cost-effectiveness model only. Excluding *ESR1-mut* testing costs is explored in scenario analysis.

B.3.5.4.2 Subsequent treatments

Subsequent treatments were included in the model as an average cost per patient, applied as a one-off cost to 95.2% of patients (representing the proportion of PFS events assumed to be progression, sourced from the EMERALD CSR) upon leaving the progression-free health state.[98] The base-case analysis setting for the distribution of subsequent treatments reflects the distribution of subsequent treatments anticipated to be administered in clinical practice. Subsequent treatments included in the model comprise ChT, namely capecitabine, docetaxel and paclitaxel.

The unit costs for subsequent treatments are shown in Table 73.

Table 73: Subsequent therapy unit drug cost

Treatment	Units (mg)	Pack size	Pack cost (£)	Source
Capecitabine	150 mg	60	£9.27	eMIT (2022)[121]
	300 mg	60	£11.60	
	500 mg	120	£25.67	
Docetaxel	20 mg	1	£3.68	
	80 mg	1	£8.17	
	160 mg	1	£16.04	
Paclitaxel	30 mg	1	£4.03	
	100 mg	1	£11.49	
	150 mg	1	£17.28	
	300 mg	1	£17.40	

Abbreviations: eMIT, (Drugs and pharmaceutical) electronic Market Information Tool

Dosing and treatment duration information was taken from the literature. Dosing information was sourced from the Breast Pathway Group for capecitabine, with treatment duration (average of 93 and 98 days) obtained from the capecitabine SmPC.[142,143] For docetaxel, the dose and treatment duration (24 weeks) were sourced from Dieras at al. (1996), and for paclitaxel, the dose and treatment duration (20.9 weeks) were sourced from the paclitaxel SmPC.[144,145]

Capecitabine is administered orally at a dose between 1,000 mg/m^2 and 1,250 mg/m^2 twice daily every three weeks on days 1 to 14. The target dose used in the model base case is an Company evidence submission for elacestrant for oestrogen receptor-positive, HER2-negative advanced breast cancer with an *ESR1-mut* after at least 1 endocrine treatment

average dose of 1,125 mg/m^2. Docetaxel is administered via intravenous (IV) infusion at a dose of 75 mg/m^2 once every three weeks. Paclitaxel is administered via intravenous (IV) infusion at a dose of 260 mg/m^2 once every three weeks.

The proportion of elacestrant patients assumed to receive subsequent treatment was sourced from EMERALD.[33] For the comparators, the proportion of patients receiving subsequent treatment was assumed equal to elacestrant.

The base case subsequent treatment distributions and duration of subsequent treatment can be found in Table 74. All patients were assumed to receive capecitabine as a subsequent treatment in the base case, though alternative assumptions were explored in scenario analyses (presented in the economic model).

Table 74: Subsequent treatment distributions and duration of treatment

Regimen	Duration (months)	Elacestrant		Everolimus + exemestane		Alpelisib + fulvestrant		Cost
		% receiving sub tx	Dist.	% receiving sub tx	Dist.	% receiving sub tx	Dist.	
Capecitabine	3.14	[redacted]	100%	[redacted]	100%	[redacted]	100%	£106.03
Docetaxel	5.52		0%		0%		0%	£2,397.74
Paclitaxel	4.81		0%		0%		0%	£2,179.16
Total cost (applied on progression)		[redacted]		[redacted]		[redacted]		

Abbreviations: Dist., distribution; sub tx, subsequent treatment.
Duration source: Capecitabine SmPC, Dieras *et al*. (2006), paclitaxel SmPC.[143–145]

B.3.5.4.3 Terminal care costs

Health and social care costs for end-of-life care are captured in the model, taken from a modelling study published by Round *et al.* (2015).[146] Each cost in Table 75 is representative of the mean estimated cost per patient. Both categories capture the direct and indirect impacts (from the initiation of strong opioids to death) associated with terminal care costs in England and Wales. Both costs have been inflated to reflect 2021/22 costs using the NHS PSSRU cost inflation index, resulting in a total end-of-life cost of £8,060.87 per patient.[123,147]

Table 75: End of life care costs

Category	Original cost	Inflated cost	Source
Health care	£4,346.00	£4,873.07	Round *et al*. (2015)
Social care	£2,843.00	£3,187.79	
Total:		£8,060.87	

B.3.6 Severity

The QALY shortfall was calculated using the R-Shiny tool by Schneider *et al.* (2021).[148] To estimate the QALY shortfall, baseline characteristics for each population were extracted from the economic model and were used to generate expected lifetime QALYs for an equivalent population without the disease. These input data are presented in Table 76. A summary list of QALY shortfall estimates from previous evaluations is not presented as there are no relevant examples of past appraisals that would be applicable to the patient population for this appraisal.

Table 76: Summary features of QALY shortfall analysis

Factor	Value		Reference to section in submission
	***ESR1-mut* and ≥12 months of prior ET + CDK4/6i population**	***ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population**	
Sex distribution (% female)	[redacted]	[redacted]	Table 39 (Section B.3.3.3)
Starting age (years)	[redacted]	[redacted]	

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; QALY, quality adjusted life years.
Note: Sex distribution and starting age rounded to 0 decimal places per the requirements of the published QALY shortfall tool.

A summary of the health state utility values and base-case analysis undiscounted life years for patients receiving everolimus + exemestane (*ESR1-mut* and ≥12 months of prior ET + CDK4/6i population) and alpelisib + fulvestrant (*ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population) are presented in Table 77.

Table 77: Summary of health state benefits and utility values for QALY shortfall analysis

Health state	Utility value: mean	Undiscounted life years	
		Everolimus + exemestane	Alpelisib + fulvestrant
Progression free	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality adjusted life years.

The total remaining discounted QALYs for patients treated with everolimus + exemestane or alpelisib + fulvestrant were taken from the cost-effectiveness model 'results' sheet (and inputted into the QALY shortfall tool to 2 decimal places). OS in the everolimus + exemestane and alpelisib + fulvestrant arms (used to estimate life years [LYs] and subsequently, QALYs) was calculated using the MAIC analysis (as described in Section B.2.9.

Results of the QALY shortfall calculator are presented in Table 78.

Within the context of this appraisal, the criteria for applying a x1.2 severity modifier/QALY weight are met for the *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population considered by the model. No severity modifier is applicable for the *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population.

Table 78: Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
[redacted]	Everolimus + exemestane	Absolute: [redacted] Proportional: [redacted] QALY weight: x1.2
[redacted]	Alpelisib + fulvestrant	Absolute: [redacted] Proportional: [redacted] QALY weight: x1

Abbreviations: QALY, quality adjusted life years.
Note: QALY shortfall for everolimus + exemestane was conducted in the *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population; QALY shortfall for alpelisib + fulvestrant was conducted in the *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population.

B.3.7 Uncertainty

Owing to the specifications of the populations relevant for this appraisal, no identified evidence was reported in the literature to support a comparison to elacestrant. While data for the comparators are available from the BOLERO-2, SOLAR-1 and BYLIEVE studies, no data are published for a population with *ESR1-mut* and ≥12 months of prior ET + CDK4/6i. Despite a lack of direct evidence available to inform a comparison to everolimus + exemestane and alpelisib + fulvestrant, the MAIC demonstrated a [redacted] for elacestrant. While the evidence from the Flatiron RWD is based on a US population, Flatiron

provides the only data for patients receiving the comparator treatment regimens for the relevant patient populations due to the lack of ESR1mut testing in the UK and other European countries and therefore provides the most robust evidence for a comparison to elacestrant.

Uncertainty in the model inputs have been tested through extensive sensitivity analyses which tested the structural and parameter uncertainty associated with elacestrant vs. both relevant comparators (everolimus + exemestane and alpelisib + fulvestrant). Sensitivity analyses are presented in the economic model and throughout Section B.3.10.

B.3.8 Summary of base-case analysis inputs and assumptions

B.3.8.1 Summary of base-case analysis inputs

A summary of variables applied in the economic model are presented in Table 79.

Table 79: Summary of base case variables applied in the economic model

Parameter	Value	Distribution	Upper, Lower bounds	Reference to section in submission
Model settings				
Time horizon (years)	37	Not varied	-	Section B.3.2.2.3
Cycle length (days)	7	Not varied	-	
Annual discount rate: Costs	3.5%	Not varied	-	
Annual discount rate: LYs	0.0%	Not varied	-	
Annual discount rate: QALYs	3.5%	Not varied	-	
Patient characteristics				
Population 1: Age (mean, years)	[redacted]	Normal	[redacted]	Section B.3.2.1
Population 2: Age (mean, years)	[redacted]	Normal	[redacted]	
Population 1: Proportion female (%)	[redacted]	Normal*	[redacted]	
Population 2: Proportion female (%)	[redacted]	Normal*	[redacted]	
Population 1: BSA (mean, m²)	[redacted]	Normal	[redacted]	
Population 2: BSA (mean, m²)	[redacted]	Normal	[redacted]	
Efficacy				
Population 1: ELA OS curve	Log-logistic	Multinormal	Using variance/covariance matrix	Section B.3.4
Population 2: ELA OS curve	Weibull			
Population 1: ELA PFS curve	Log-normal			
Population 2: ELA PFS curve	Log-normal			
Population 1: ELA TTD curve	KM	Not varied	-	
Population 2: ELA TTD curve	KM	Not varied	-	
EVE+EXE OS curve	Gamma	Multinormal	Using variance/covariance matrix	
ALP+FUL OS curve	Gamma			
EVE+EXE PFS curve	Log-normal			
ALP+FUL PFS curve	Log-normal			

Treatment costs				
Elacestrant (345mg)	[redacted]	Not varied	-	Section B.3.5.1.1
Elacestrant (86mg)	[redacted]	Not varied	-	
Everolimus (2.5mg)	£1,020.00	Normal	£951.20, £1,219.92	
Everolimus (5mg)	£1,912.50	Normal	£1,783.50, £2,287.34	
Everolimus (10mg)	£2,272.05	Normal	£2,118.80, £2,717.36	
Exemestane	£4.25	Normal	£3.97, £5.09	
Alpelisib (150mg)	£4,082.14	Not varied	-	
Alpelisib (200mg)	£4,082.14	Not varied	-	
Fulvestrant	£80.18	Normal	£74.77, £95.89	
RDI: Elacestrant	[redacted]	Normal	[redacted]	Section B.3.5.1.1
RDI: Everolimus	98.0%	Normal	91.39%, 100%	
RDI: Exemestane	100.0%	Normal	93.26%, 100%	
RDI: Alpelisib	94.0%	Normal	87.66%, 100%	
RDI: Fulvestrant	94.0%	Normal	87.66%, 100%	
Administration costs				
IM injection	£8.67	Normal	£8.08, £10.37	Section B.3.5.1.2
IV administration	£286.71	Normal	£267.37, £342.90	
Healthcare resource use costs				
Cost: GP visit	£41.00	Normal	£38.23, £49.04	Section B.3.5.2
Cost: Oncology specialist visit	£188.57	Normal	£175.85, £225.53	
Cost: Community nurse	£52.00	Normal	£48.49, £62.19	
Cost: Clinical nurse specialist	£63.00	Normal	£58.75, £75.35	
Cost: Social worker	£50.00	Normal	£46.63, £59.8	
Cost: Physiotherapist	£48.50	Normal	£45.23, £58.01	
Cost: CT scan	£142.47	Normal	£132.86, £170.4	
Cost: Lymphoedema nurse	£53.00	Normal	£49.43, £63.39	

Freq: GP visit – PF	0.23	Normal	0.21, 0.28	
Freq: Oncology specialist visit – PF	0.04	Normal	0.04, 0.05	
Freq: Community nurse – PF	0.08	Normal	0.07, 0.09	
Freq: Clinical nurse specialist – PF	0.23	Normal	0.21, 0.28	
Freq: Social worker – PF	0.11	Normal	0.11, 0.14	
Freq: Physiotherapist – PF	0.00	Normal	0, 0	
Freq: CT scan – PF	0.08	Normal	0.07, 0.09	
Freq: Lymphoedema nurse – PF	0.00	Normal	0, 0	
Freq: GP visit – PP	0.34	Normal	0.32, 0.41	
Freq: Oncology specialist visit – PP	0.11	Normal	0.11, 0.14	
Freq: Community nurse – PP	0.15	Normal	0.14, 0.18	
Freq: Clinical nurse specialist – PP	0.46	Normal	0.43, 0.55	
Freq: Social worker – PP	0.11	Normal	0.11, 0.14	
Freq: Physiotherapist – PP	0.11	Normal	0.11, 0.14	
Freq: CT scan – PP	0.08	Normal	0.07, 0.09	
Freq: Lymphoedema nurse – PP	0.11	Normal	0.11, 0.14	
***ESR1* mutation testing**				
Proportion with *ESR1-mut*	50.0%	Beta	40.22%, 59.78%	Section B.3.5.4.1
ESR1-mut test cost	£300.00	Normal	£279.77, £358.80	
Subsequent treatments				
Drug cost: Capecitabine (150mg)	£9.27	Normal	£8.64, £11.09	Section B.3.5.4.2
Drug cost: Capecitabine (300mg)	£11.60	Normal	£10.82, £13.87	
Drug cost: Capecitabine (500mg)	£25.67	Normal	£23.94, £30.7	
Drug cost: Docetaxel (20mg)	£3.68	Normal	£3.43, £4.4	
Drug cost: Docetaxel (80mg)	£8.17	Normal	£7.62, £9.77	
Drug cost: Docetaxel (160mg)	£16.04	Normal	£14.96, £19.18	
Drug cost: Paclitaxel (30mg)	£4.03	Normal	£3.76, £4.82	

Drug cost: Paclitaxel (100mg)	£11.49	Normal	£10.71, £13.74	
Drug cost: Paclitaxel (150mg)	£17.28	Normal	£16.11, £20.67	
Drug cost: Paclitaxel (300mg)	£17.40	Normal	£16.23, £20.81	
Prop. of PFS events assumed to be progression	95.2%	Beta	65.22%, 100%	
Duration: Capecitabine	3.14	Normal	2.93, 3.75	
Duration: Docetaxel	5.52	Normal	5.15, 6.6	
Duration: Paclitaxel	4.81	Normal	4.48, 5.75	
Number receiving sub tx: ELA	[redacted]	Normal	[redacted]	
Number receiving sub tx: EVE + EXE	[redacted]	Normal	[redacted]	
Number receiving sub tx: ALP + FUL	[redacted]	Normal	[redacted]	
Sub tx distribution: ELA – Capecitabine	100.0%	Dirichlet		
Sub tx distribution: ELA – Docetaxel	0.0%			
Sub tx distribution: ELA – Paclitaxel	0.0%			
Sub tx distribution: EVE + EXE – Capecitabine	100.0%	Dirichlet		
Sub tx distribution: EVE + EXE – Docetaxel	0.0%			
Sub tx distribution: EVE + EXE – Paclitaxel	0.0%			
Sub tx distribution: ALP + FUL – Capecitabine	100.0%	Dirichlet		
Sub tx distribution: ALP + FUL – Docetaxel	0.0%			
Sub tx distribution: ALP + FUL – Paclitaxel	0.0%			
Adverse event frequency				
AE freq: Anaemia – ELA	1.7%	Beta	2.09%, 3.09%	Section B.3.4.4
AE freq: ALT increase – ELA	0.9%	Beta	1.04%, 1.55%	
AE freq: AST increase – ELA	1.7%	Beta	2.09%, 3.09%	
AE freq: Asthenia – ELA	2.6%	Beta	2.09%, 3.09%	
AE freq: Back pain – ELA	4.3%	Beta	3.13%, 4.63%	
AE freq: Bone pain – ELA	2.6%	Beta	2.09%, 3.09%	
AE freq: Diarrhoea – ELA	0.0%	Beta	0%, 0%	

AE freq: Dyspnoea – ELA	0.0%	Beta	0%, 0%	
AE freq: Fatigue – ELA	1.7%	Beta	2.09%, 3.09%	
AE freq: Hyperglycaemia – ELA	0.0%	Beta	0%, 0%	
AE freq: Mucosal inflammation – ELA	0.0%	Beta	0%, 0%	
AE freq: Nausea – ELA	4.3%	Beta	4.17%, 6.18%	
AE freq: Pneumonitis – ELA	0.9%	Beta	0%, 0%	
AE freq: Rash – ELA	0.9%	Beta	0%, 0%	
AE freq: Stomatitis – ELA	0.0%	Beta	0%, 0%	
AE freq: Thrombocytopenia – ELA	0.0%	Beta	0%, 0%	
AE freq: Vomiting – ELA	1.7%	Beta	0%, 0%	
AE freq: Anaemia – EVE+EXE	6.0%	Beta	4.88%, 7.23%	
AE freq: ALT increase – EVE+EXE	3.0%	Beta	2.44%, 3.61%	
AE freq: AST increase – EVE+EXE	3.0%	Beta	2.44%, 3.61%	
AE freq: Asthenia – EVE+EXE	2.0%	Beta	1.63%, 2.41%	
AE freq: Back pain – EVE+EXE	0.0%	Beta	0%, 0%	
AE freq: Bone pain – EVE+EXE	0.0%	Beta	0%, 0%	
AE freq: Diarrhoea – EVE+EXE	2.0%	Beta	1.63%, 2.41%	
AE freq: Dyspnoea – EVE+EXE	4.0%	Beta	3.25%, 4.82%	
AE freq: Fatigue – EVE+EXE	3.0%	Beta	2.44%, 3.61%	
AE freq: Hyperglycaemia – EVE+EXE	4.0%	Beta	3.25%, 4.82%	
AE freq: Mucosal inflammation – EVE+EXE	0.0%	Beta	0%, 0%	
AE freq: Nausea – EVE+EXE	0.0%	Beta	0%, 0%	
AE freq: Pneumonitis – EVE+EXE	3.0%	Beta	2.44%, 3.61%	
AE freq: Rash – EVE+EXE	1.0%	Beta	0.81%, 1.21%	
AE freq: Stomatitis – EVE+EXE	8.0%	Beta	6.50%, 9.64%	
AE freq: Thrombocytopenia – EVE+EXE	3.0%	Beta	2.44%, 3.61%	
AE freq: Vomiting – EVE+EXE	0.0%	Beta	0%, 0%	

AE freq: Anaemia – ALP+FUL	0.0%	Beta	0%, 0%	
AE freq: ALT increase – ALP+FUL	0.0%	Beta	0%, 0%	
AE freq: AST increase – ALP+FUL	0.0%	Beta	0%, 0%	
AE freq: Asthenia – ALP+FUL	1.8%	Beta	1.43%, 2.12%	
AE freq: Back pain – ALP+FUL	0.0%	Beta	0%, 0%	
AE freq: Bone pain – ALP+FUL	0.0%	Beta	0%, 0%	
AE freq: Diarrhoea – ALP+FUL	6.7%	Beta	5.44%, 8.06%	
AE freq: Dyspnoea – ALP+FUL	0.0%	Beta	0%, 0%	
AE freq: Fatigue – ALP+FUL	3.5%	Beta	2.86%, 4.24%	
AE freq: Hyperglycaemia – ALP+FUL	36.6%	Beta	29.6%, 43.93%	
AE freq: Mucosal inflammation – ALP+FUL	2.1%	Beta	1.72%, 2.55%	
AE freq: Nausea – ALP+FUL	2.5%	Beta	2%, 2.97%	
AE freq: Pneumonitis – ALP+FUL	0.0%	Beta	0%, 0%	
AE freq: Rash – ALP+FUL	9.9%	Beta	8.01%, 11.87%	
AE freq: Stomatitis – ALP+FUL	2.5%	Beta	2.0%, 2.97%	
AE freq: Thrombocytopenia – ALP+FUL	0.0%	Beta	0%, 0%	
AE freq: Vomiting – ALP+FUL	0.7%	Beta	0.57%, 0.85%	
Adverse event costs				
AE cost: Anaemia	£2,015.26	Normal	£1,879.34, £2,410.25	Section B.3.5.3
AE cost: ALT increase	£2,214.32	Normal	£2,064.97, £2,648.32	
AE cost: AST increase	£2,214.32	Normal	£2,064.97, £2,648.32	
AE cost: Asthenia	£2,015.26	Normal	£1,879.34, £2,410.25	
AE cost: Back pain	£1,186.77	Normal	£1,106.72, £1,419.37	
AE cost: Bone pain	£1,273.43	Normal	£1,187.51, £1,523.02	
AE cost: Diarrhoea	£1,746.82	Normal	£1,629.00, £2,089.19	
AE cost: Dyspnoea	£862.68	Normal	£804.49, £1,031.76	
AE cost: Fatigue	£2,015.26	Normal	£1,879.34, £2,410.25	

AE cost: Hyperglycaemia	£1,365.50	Normal	£1,273.40, £1,633.13	
AE cost: Mucosal inflammation	£1,746.82	Normal	£1,629.00, £2,089.19	
AE cost: Nausea	£1,746.82	Normal	£1,629.00, £2,089.19	
AE cost: Pneumonitis	£862.68	Normal	£804.49, £1,031.76	
AE cost: Rash	£1,902.34	Normal	£1,774.03, £2,275.19	
AE cost: Stomatitis	£1,746.82	Normal	£1,629.00, £2,089.19	
AE cost: Thrombocytopenia	£993.37	Normal	£926.37, £1,188.07	
AE cost: Vomiting	£1,746.82	Normal	£1,629.00, £2,089.19	
Terminal care costs				
Terminal care cost: Health care	£4,873.07	Normal	£4,544.39, £5,828.18	Section B.3.5.4.3
Terminal care cost: Social care	£3,187.79	Normal	£2,972.78, £3,812.59	
Health state utility values				
HSUV: Progression-free	[redacted]	Beta	[redacted]	Section B.3.4.5
HSUV: Progressed disease	[redacted]	Beta	[redacted]	
General population utility – coefficients				
Male	0.021213	Multinormal (using variance/covariance matrix)		Section B.3.4.5
Age	-0.000259			
Age²	-0.000033			
Constant	0.950857			

Abbreviations: AE, adverse event; ALP, alpelisib; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BSA, body surface area; CT, computed tomography; ELA, elacestrant; *ESR1*, oestrogen receptor 1 gene; EVE, everolimus; EXE, exemestane; Freq., frequency; FUL, fulvestrant; GP, general practitioner; HSUV, health state utility values; IM, Intramuscular; IV, intravenous; KM, Kaplan-Meier; LY, life year; OS, overall survival, PF, progression-free; PFS, progression-free survival; PP, post-progression; QALY, quality-adjusted life year; RDI, relative dose intensity; Sub tx, subsequent treatment; TTD, time to treatment discontinuation.
Note: *Upper bound capped at 100%

B.3.8.2 Assumptions

Table 80 present a summary of key modelling assumptions.

Table 80: Summary of key modelling assumptions

Assumption	Description	Justification
Model settings		
Time horizon	37 years constitutes a lifetime horizon.	>99% of the modelled cohort have entered the death state by 37 years, across treatment arms.
Cycle length	A weekly cycle length with no half-cycle correction.	This relatively short cycle length is considered appropriate due to the poor prognosis of patients with advanced/metastatic mBC, frequently resulting in rapid disease progression. Due to the short cycle length, half-cycle correction is not required.
Patient characteristics	Based on the baseline patient characteristics from EMERALD.	Baseline patient characteristics for the relevant populations from EMERALD were assumed to be generalisable to the UK population.
Parametric survival analysis		
Elacestrant (OS, PFS)	EMERALD data MAIC-weighted to match each comparator population. Extrapolated with: • *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population: OS - Log-logistic, PFS - Log-normal • *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population: OS - Weibull, PFS - Log-normal	Based on clinical plausibility of the long-term extrapolations, statistical goodness-of-fit and visual fit. Alternative parametric models are tested in scenario analysis.
Comparators (OS, PFS)	Flatiron data. Extrapolated with: • *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population: OS - Gamma, PFS - Log-normal • *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population: OS - Gamma, PFS - Log-normal	Based on clinical plausibility of the long-term extrapolations, statistical goodness-of-fit and visual fit. Alternative parametric models are tested in scenario analysis.
Time to treatment discontinuation		
Elacestrant TTD	EMERALD data MAIC-weighted to match each comparator population. KM curve used to estimate TTD.	Based on data maturity, the TTD curve accurately captures the time spent on treatment with elacestrant. Alternative parametric models are tested in scenario analyses.
Comparator TTD	Assumed equal to PFS.	Lack of available data from the Flatiron database and the literature.
Indirect comparison		

ITC	MAIC conducted based on available prognostic factors and treatment effect modifiers from EMERALD and Flatiron	No evidence was identified to inform comparator efficacy in the relevant patient populations. Therefore, evidence was sought from the real-world Flatiron database.
Comparative efficacy	Independent parametric survival models fitted to MAIC-adjusted EMERALD data for elacestrant and digitised Flatiron data for the comparators.	The proportional hazards (PH) assumption was explored to assess the suitability of applying the MAIC hazard ratios (HRs) to the elacestrant data to estimate OS and PFS for the comparators. As the PH assumption appeared to be violated, independent models were fit to elacestrant and the comparators for all outcomes. Efficacy informed by the MAIC HRs is explored in scenario analysis.
ESR1-mut testing costs	£300	Based on a dPCR test
Subsequent treatments	All treatments are assumed to receive chemotherapy after treatment discontinuation.	Chemotherapy is considered to be the only treatment option for patients in either population following discontinuation. Retreatment with CDK4/6i is not reimbursed in the UK. Similarly, alpelisib + fulvestrant is only recommended at the second line and thus, would not be a subsequent therapy option.
Utilities	Utility values were estimated from EQ-5D-5L data from the EMERALD trial (using the UK tariff), mapped onto the EQ-5D-3L[25]	In line with the NICE reference case. Progressed utilities from Lloyd *et al*. (2006) are explored in scenario analyses. [76]
Adverse events		
Incidence	The incidence of treatment-related, grade ≥3 AEs, affecting ≥2% of patients for any relevant comparator, were modelled (irrespective of the incidence being <2% for other comparators).	Grade ≥3 AEs are expected to have the greatest impact on patients.
Disutilities	AE disutilities are excluded from the base case.	AE disutilities are excluded from the base case owing to the inclusion of AEs in the utility estimation from EMERALD. Inclusion of AE disutilities are explored in scenario analysis.

Abbreviations: AE, adverse event; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; dPCR, digital polymerase chain reaction; EQ-XD, Euro-QoL X-dimension; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; HR, hazard ratio; ITC, indirect treatment comparison; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; mBC, metastatic Breast Cancer; NICE, National Institute for Health and Care Excellence; OS, overall survival, PFS, progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PH, proportional hazards; TTD, time to treatment discontinuation.

B.3.9 Base-case results

Base case deterministic results including the fixed PAS price are presented in Table 81 with net-health benefit (NHB) results provided in Table 83 (at willingness-to-pay [WTP] thresholds of £20,000 and £30,000 per QALY gained). Results are provided for both populations: *ESR1-mut* + ≥12 months of prior ET + CDK4/6i, and *ESR1-mut, PIK3CA-mut* + ≥12 months of prior ET + CDK4/6i.

The NICE manual states cost-effectiveness estimates should be derived from a probabilistic analysis, when possible. Therefore, results are presented using probabilistic results Table 82 and Table 84.

When considering a x1.2 QALY weight gain for the *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population (Section B.3.6), the base case results demonstrate that elacestrant is associated with a deterministic ICER of £24,893 and a probabilistic ICER of £24,227 versus everolimus + exemestane.

Considering no severity modifier for the *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population (Section B.3.6), the base case results demonstrate that elacestrant is associated with deterministic incremental costs and QALYs of -£12,269 and 0.277 and probabilistic incremental costs and QALYs of -£12,506 and 0.276 versus alpelisib + fulvestrant.

Table 81: Base-case results (deterministic) – Fixed PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs*	ICER versus baseline (£/QALY)	Incremental NMB (£, £30,000/QALY)
***ESR1-mut* and ≥12 months of prior ET + CDK4/6i**								
Everolimus + exemestane	[redacted]	[redacted]	[redacted]					
Elacestrant	[redacted]	[redacted]	[redacted]	£18,883	1.107	0.759	£24,893	3,874
***ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i**								
Alpelisib + fulvestrant	[redacted]	[redacted]	[redacted]					
Elacestrant	[redacted]	[redacted]	[redacted]	-£12,269	0.430	0.277	Dominant	£20,570

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; PAS, patient access scheme; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; QALYs, quality-adjusted life years. Note: *A severity modifier of 1.2 is applied to the discounted incremental QALYs.

Table 82: Base-case results (probabilistic) – Fixed PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs*	ICER versus baseline (£/QALY)	Incremental NMB (£, £30,000/QALY)
***ESR1-mut* and ≥12 months of prior ET + CDK4/6i**								
Everolimus + exemestane	[redacted]	[redacted]	[redacted]					
Elacestrant	[redacted]	[redacted]	[redacted]	£18,307	1.100	0.756	£24,227	4,362
***ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i**								
Alpelisib + fulvestrant	[redacted]	[redacted]	[redacted]					
Elacestrant	[redacted]	[redacted]	[redacted]	-£12,506	0.429	0.276	Dominant	£20,798

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; PAS, patient access scheme; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; QALYs, quality-adjusted life years.
Note: *A severity modifier of 1.2 is applied to the discounted incremental QALYs.

Table 83: Net health benefit (deterministic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
***ESR1-mut and* ≥12 months of prior ET + CDK4/6i**						
Everolimus + exemestane	[redacted]	[redacted]				
Elacestrant	[redacted]	[redacted]	18,883	0.759	-0.186	0.129
***ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i**						
Alpelisib + fulvestrant	[redacted]	[redacted]				
Elacestrant	[redacted]	[redacted]	-12,269	0.277	0.890	0.686

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; NHB, net health benefit; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; QALYs, quality-adjusted life years.
Note: *A severity modifier of 1.2 is applied to the discounted incremental QALYs.

Table 84: Net health benefit (probabilistic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
***ESR1-mut and* ≥12 months of prior ET + CDK4/6i**						
Everolimus + exemestane	[redacted]	[redacted]				
Elacestrant	[redacted]	[redacted]	18,307	0.756	-0.160	0.145
***ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i**						
Alpelisib + fulvestrant	[redacted]	[redacted]				
Elacestrant	[redacted]	[redacted]	-12,506	0.276	0.902	0.693

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; NHB, net health benefit; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; QALYs, quality-adjusted life years.
Note: *A severity modifier of 1.2 is applied to the discounted incremental QALYs.

B.3.10 Exploring uncertainty

B.3.10.1 Probabilistic sensitivity analysis

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA). In PSA, all parameters are simultaneously varied from an assigned probability distribution (see Table 79). PSA inputs were randomly drawn, and results recorded across 5,000 iterations, by which point costs and outcomes had stabilised and were considered reliable for capturing uncertainty (assessed by visual inspection of convergence plots in the submitted cost-effectiveness model).

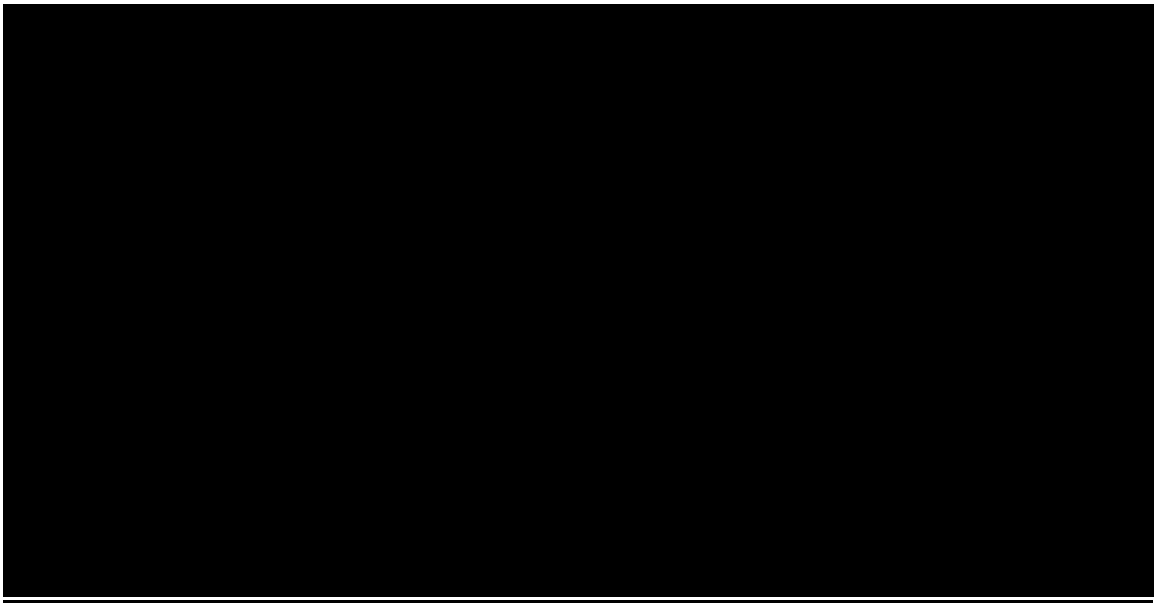
Mean probabilistic results are presented in Table 82 and Table 84. Figure 48 and Figure 49 presents the cost-effectiveness acceptability curves for elacestrant versus everolimus + exemestane and alpelisib + fulvestrant, respectively. At a WTP threshold of £30,000 per QALY gained, elacestrant has the highest probability of being the most cost-effective option for both populations (when considering the x1.2 severity modifier for the *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population).

Figure 50 and Figure 51 present an incremental cost-effectiveness plane for elacestrant versus everolimus + exemestane and alpelisib + fulvestrant, respectively. Of 5,000 PSA iterations, [redacted] and [redacted] indicate that elacestrant provides more QALYs at an increased cost per patient compared to everolimus + exemestane and alpelisib + fulvestrant, respectively.

Figure 48: Cost-effectiveness acceptability curve | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ELA, elacestrant; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; EVE, everolimus; EXE, exemestane; NMB, net monetary benefit.
Note: A severity modifier of 1.2 is applied to the discounted incremental QALYs.

Figure 49: Cost-effectiveness acceptability curve | *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i



Abbreviations: ALP, alpelisib; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ELA, elacestrant; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; FUL, fulvestrant; NMB, net monetary benefit; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Figure 50: Incremental cost-effectiveness plane | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; ELA, elacestrant; EVE, everolimus; EXE, exemestane; QALY, quality-adjusted life year; WTP, willingness-to-pay.
Note: A severity modifier of 1.2 is applied to the discounted incremental QALYs.

Figure 51: Incremental cost-effectiveness plane | *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i

Abbreviations: ALP, alpelisib; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ELA, elacestrant; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; FUL, fulvestrant; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; QALY, quality-adjusted life year; WTP, willingness-to-pay.

B.3.10.2 Deterministic sensitivity analysis

One-way sensitivity analysis (OWSA) was conducted to test the impact of individual parameter uncertainty on cost-effectiveness results, holding all else constant. In turn, inputs were set to their respective lower and upper limits (presented in Table 79), while all other parameters were maintained at their base case setting. If the variance of a parameter was not available, a simplifying assumption was made assuming that the standard error was 10% of the mean values. Correlated inputs with joint uncertainty, such as parametric survival model coefficients which are varied in PSA using a multivariate normal distribution, were not included in the OWSA.

Figure 52 and Figure 53 present the tornado plots showing the 10 parameters with the largest impact on the incremental net-monetary benefit (INMB) for elacestrant versus everolimus + exemestane and alpelisib + fulvestrant, respectively, at a willingness-to-pay threshold of £30,000.

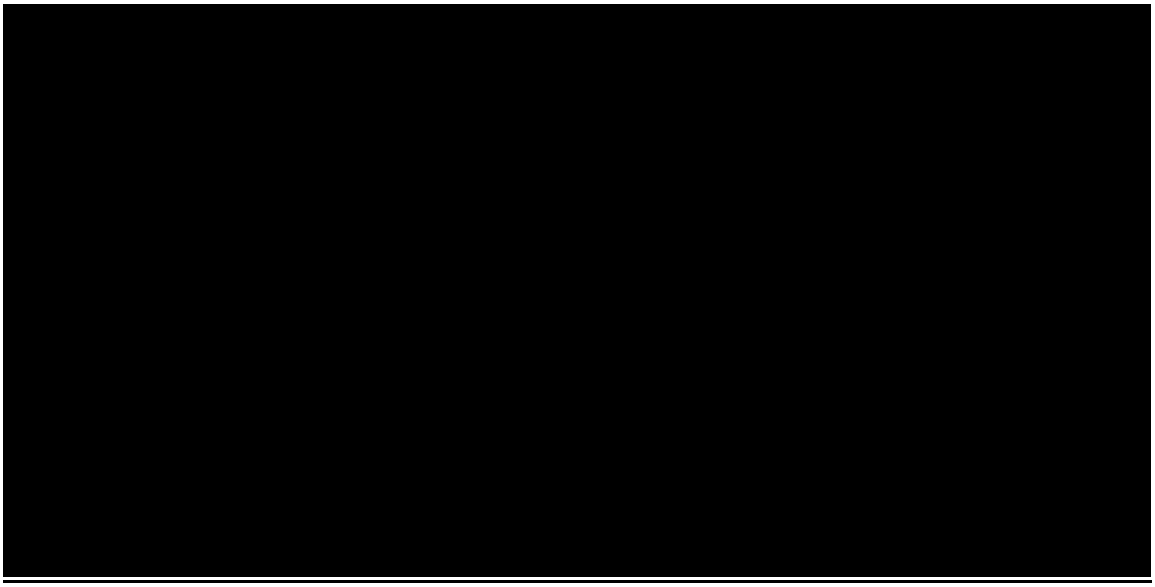
For the *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population, the OWSA demonstrates that model findings are robust to reasonable variation in parameters, with the cost of everolimus, RDI and age having the largest impact on the results.

Figure 52: Tornado plot of OWSA results (INMB) | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; HSUV, health state utility value; INMB, incremental net-monetary benefit; OWSA, one-way sensitivity analysis; PD, progressed disease; PF, progression free; QALY, quality-adjusted life year; RDI, relative dose intensity; tx, treatment; WTP, willingness-to-pay.
Note: INMB calculated using a WTP threshold of £30,000 per QALY gained. A severity modifier of 1.2 is applied to the discounted incremental QALYs. Correlated inputs with joint uncertainty (such as parametric survival model coefficients) are not included in the OWSA.

For the *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i population, the parameter with the largest impact on the INMB was RDI for alpelisib and elacestrant. As seen with the comparison to everolimus + exemestane, the OWSA versus alpelisib + fulvestrant demonstrates the model findings are robust to reasonable variation in parameters.

Figure 53: Tornado plot of OWSA results (INMB) | *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i



Abbreviations: ALP, alpelisib; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; FUL, fulvestrant; HSUV, health state utility value; INMB, incremental net-monetary benefit; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PD, progressed disease; PF, progression free; OWSA, one-way sensitivity analysis; QALY, quality-adjusted life year RDI, relative dose intensity; tx, treatment; WTP, willingness-to-pay.
Note: INMB calculated using a WTP threshold of £30,000 per QALY gained. Correlated inputs with joint uncertainty (such as parametric survival model coefficients) are not included in the OWSA.

B.3.10.3 Scenario analysis

Scenario analyses were performed to test key structural and methodological assumptions within the model. As the base case probabilistic results and deterministic results were close, scenario analyses were conducted deterministically. Results of the scenario analyses are presented in Table 85 and Table 86 compared to everolimus + exemestane and alpelisib + fulvestrant, respectively. All scenarios presented for the *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population met the x1.2 severity modifier criteria.

Table 85: Scenario analysis results | *ESR1-mut* and ≥12 months of prior ET + CDK4/6i – elacestrant versus everolimus + exemestane

Parameter/setting	Base case	Scenario	ICER	NMB
Time horizon	37 years	10 years	£28,135	£1,190
		20 years	£25,379	£3,403
Discount rates for costs and QALYs	3.5%	1.5%	£23,310	£5,665
		6.0%	£26,770	£2,174
MAIC approach	Independent PSM extrapolation	HR	£27,070	£2,135
Elacestrant OS	Log-logistic	Gamma	£43,793	-£5,257
		Log-normal	£22,380	£6,674

Everolimus + exemestane OS	Gamma	Weibull	£25,087	£3,697
		Exponential	£26,248	£2,669
Elacestrant PFS	Log-normal	Log-logistic	£24,609	£4,099
Everolimus + exemestane PFS	Log-normal	Log-logistic	£24,530	£4,147
		Gamma	£25,678	£3,283
Elacestrant TTD	KM curve	Log-normal	£22,618	£5,600
		Log-logistic	£22,451	£5,726
RDI	Include	Exclude	£24,968	£3,817
ESR1-mut testing costs	Include	Exclude	£24,102	£4,474
Subsequent treatment costs	Include	Exclude	£24,896	£3,872
Progressed utility source	EMERALD EQ-5D analysis ([redacted])	Lloyd *et al*. (2006), absolute approach (0.601)	£26,097	£2,824
Age-adjusted utilities	Enabled	Disabled	£24,037	£4,684
AE disutilities	Exclude	Include	£24,852	£3,912

Abbreviations: AE, adverse event; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; EQ-XD, Euro-QoL X-dimension; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; INMB, incremental net-monetary benefit; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; PSM, parametric survival model; NMB, net-monetary benefit; QALY, quality-adjusted life year; RDI, relative dose intensity; TTD, time to treatment discontinuation; WTP, willingness-to-pay.
Note: INMB calculated using a WTP threshold of £30,000 per QALY gained. A severity modifier of 1.2 is applied to the discounted incremental QALYs.

Table 86: Scenario analysis results | *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i – elacestrant versus alpelisib + fulvestrant

Parameter/setting	Base case	Scenario	ICER	NMB
Time horizon	37 years	10 years	Dominant	£20,580
		20 years	Dominant	£20,570
Discount rates for costs and QALYs	3.5%	1.5%	Dominant	£20,977
		6.0%	Dominant	£20,090
MAIC approach	Independent PSM extrapolation	HR	Dominant	£19,341
Elacestrant OS	Weibull	Gamma	Dominant	£25,522
		Log-normal	Dominant	£38,372
Alpelisib + fulvestrant OS	Gamma	Weibull	Dominant	£21,943
		Log-normal	Dominant	£15,437
Elacestrant PFS	Log-normal	Log-logistic	Dominant	£20,534
		Exponential	Dominant	£20,970
Alpelisib + fulvestrant PFS	Log-normal	Generalised gamma	Dominant	£22,166
		Gamma	Dominant	£20,290

Elacestrant TTD	KM curve	Log-normal	Dominant	£23,300
		Log-logistic	Dominant	£26,025
RDI	Include	Exclude	Dominant	£22,725
ESR1-mut testing costs	Include	Exclude	Dominant	£21,170
Subsequent treatment costs	Include	Exclude	Dominant	£20,570
Progressed utility source	EMERALD EQ-5D analysis ([redacted])	Lloyd *et al*. (2006), absolute approach (0.601)	Dominant	£19,664
Age-adjusted utilities	Enabled	Disabled	Dominant	£20,701
AE disutilities	Exclude	Include	Dominant	£20,600

Abbreviations: AE, adverse event; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; EQ-XD, Euro-QoL X-dimension; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; INMB, incremental net-monetary benefit; MAIC, matching-adjusted indirect comparison; NMB, net-monetary benefit; OS, overall survival; PFS, progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PSM, parametric survival model; QALY, quality-adjusted life year; RDI, relative dose intensity; TTD, time to treatment discontinuation; WTP, willingness-to-pay.
Note: INMB calculated using a WTP threshold of £30,000 per QALY gained.

B.3.11 Subgroup analysis

Other than the two subgroup analyses presented throughout Section B.3 of the submission, there are no further subgroup analyses relevant to this appraisal.

B.3.12 Benefits not captured in the QALY calculation

The QALY calculation estimated as part of this submission captures the majority of benefits directly related to the patient such as delayed progression, extension to life and improved quality-of-life.

Benefits not captured by the QALY are outlined in the full submission.

Elacestrant is dosed orally, avoiding the pain and adverse events associated with the injection of fulvestrant. Adverse events associated with elacestrant are tolerable and manageable, which means that relatively few patients in the phase III study required either dose reduction or cessation of treatment.[33] This is unlike the other treatments available (everolimus + exemestane, or alpelisib + fulvestrant) where dose reductions and discontinuation due to toxicities are required.[22,25] Lastly, the introduction of ctDNA genomic testing for *ESR1-mut* at disease progression, will facilitate the identification of patients, urgently in need of a treatment specifically tailored to and active in the presence of an *ESR1-mut* (elacestrant).

B.3.13 Validation

B.3.13.1 Validation of cost-effectiveness analysis

There is no published literature reporting OS and PFS estimates for everolimus + exemestane and alpelisib + fulvestrant for the *ESR1-mut* and ≥12 months of prior ET + CDK4/6i population and *ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i populations, respectively. As such, the company were unable to compare the model estimates with reported outcomes.

Prior to submission, the cost-effectiveness model (Microsoft Excel® workbook) was quality assured as part of the internal processes of the external analysts who built the model. As part of this quality-control process, the model was reviewed for potential coding errors, inconsistencies, and the plausibility of inputs by an economist who was not involved in the model development process. The review comprised of a sheet-by-sheet check and a checklist (based on publicly available and peer review checklists). Examples of the basic validity checks followed included:

- Extreme value testing (e.g., how do results change if the time horizon is set to be as short or as long as possible?)
- Logical relationship testing (e.g., if intervention drug costs are increased, do total costs in the intervention arm increase, and is the impact on the ICER in line with expectations?)
- Consistency checks (e.g., is an input parameter value in one cell reflected elsewhere/used consistently throughout the model?)

B.3.14 Interpretation and conclusions of economic evidence

Data concerning the safety and efficacy of elacestrant are available from the pivotal EMERALD study – a phase III, international, multicentre, open-label, RCT, comparing elacestrant with international SOC endocrine monotherapy, in people with ER+/HER2-, locally advanced or mBC with an activating *ESR1-mut* who have disease progression following at least one line of ET including a CDK4/6i.[27] As endocrine monotherapy is not routinely used in the UK practice, the cost-effectiveness analysis relies upon an indirect comparison to real-world evidence for two alternative comparator regimens: everolimus in combination with exemestane, and alpelisib in combination with fulvestrant.

The cost-effectiveness analysis considers a three-state partitioned-survival analysis structure, informed by survival models fitted to the key efficacy endpoints of OS and PFS. HRQoL data were collected in EMERALD and used to inform the model, supported by data reported in the literature. Key cost categories included drug acquisition and administration, routine monitoring, resolution of adverse events, use of subsequent treatments, and end-of-life care. Key uncertainties were explored via a range of sensitivity analyses.

In the base-case analysis, including the proposed Patient Access Scheme discount, elacestrant was associated with incremental costs of £18,857 and a QALY gain of 0.757 versus everolimus + exemestane, resulting in an incremental cost-effectiveness ratio (ICER) of £24,897 per QALY gained. Compared to alpelisib + fulvestrant, elacestrant was associated with incremental costs of –£12,149 and a QALY gain of 0.277. Sensitivity analyses demonstrated consistent results, with key drivers of cost-effectiveness based on the results of the indirect comparisons, long-term survival assumptions, and utility values.

Elacestrant is the first and only approved treatment for people with ER+/HER2-, *ESR1-mut*, advanced or mBC, following ET in the advanced or metastatic setting. As the first orally administered SERD, the introduction of elacestrant into NHS practice would represent an important step change in the management of patients with *ESR1-mut* mBC – a population for whom current treatment options are associated with limited clinical benefit, high discontinuation rates due to significant toxicity, and poor prognosis (as reflected by the severity modifier calculations presented in this submission). The economic analysis presented within this submission demonstrates the cost-effectiveness of elacestrant for use Company evidence submission for elacestrant for oestrogen receptor-positive, HER2-negative advanced breast cancer with an *ESR1-mut* after at least 1 endocrine treatment

in the NHS, and provides patients with a personalised, tailored treatment option with minimal disruption to daily activities due to its oral route of administration.

References

1. Valachis A, Carlqvist P, Ma Y, Szilcz M, Freilich J, Vertuani S, et al. Overall survival of patients with metastatic breast cancer in Sweden: a nationwide study. Br J Cancer. 2022 Sep;127(4):720–5.

2. Grinda T, Antoine A, Jacot W, Blaye C, Cottu PH, Diéras V, et al. Evolution of overall survival and receipt of new therapies by subtype among 20 446 metastatic breast cancer patients in the 2008-2017 ESME cohort. ESMO Open. 2021 Jun;6(3):100114.

3. Kurosky SK, Mitra D, Zanotti G, Kaye JA. Treatment Patterns and Outcomes of Patients With Metastatic ER+/HER-2- Breast Cancer: A Multicountry Retrospective Medical Record Review. Clin Breast Cancer. 2018 Aug;18(4):e529–38.

4. Globocan. Cancer populations factsheet: United Kingdom [Internet]. World Health Organization: International Agency for Research on Cancer; 2022 [cited 2024 Apr 5]. Available from: https://gco.iarc.who.int/media/globocan/factsheets/populations/826-united-kingdom-fact-sheet.pdf

5. NHS. NHS conditions: Breast cancer in women (causes) [Internet]. [cited 2023 Aug 10]. Available from: https://www.nhs.uk/conditions/breast-cancer/causes/

6. SEER. Cancer Stat Facts: Female Breast Cancer Subtypes [Internet]. [cited 2023 Aug 10]. Available from: https://seer.cancer.gov/statfacts/html/breast-subtypes.html

7. Galipeau N, Klooster B, Krohe M, Tang DH, Revicki DA, Cella D. Understanding key symptoms, side effects, and impacts of HR+/HER2- advanced breast cancer: qualitative study findings. J Patient-Rep Outcomes. 2019 Feb 7;3:10.

8. Reed E, Simmonds P, Haviland J, Corner J. Quality of life and experience of care in women with metastatic breast cancer: a cross-sectional survey. J Pain Symptom Manage. 2012 Apr;43(4):747–58.

9. Girgis A, Lambert S, Johnson C, Waller A, Currow D. Physical, Psychosocial, Relationship, and Economic Burden of Caring for People With Cancer: A Review. J Oncol Pract. 2013 Jul;9(4):197–202.

10. Grunfeld E, Coyle D, Whelan T, Clinch J, Reyno L, Earle CC, et al. Family caregiver burden: results of a longitudinal study of breast cancer patients and their principal caregivers. CMAJ Can Med Assoc J J Assoc Medicale Can. 2004 Jun 8;170(12):1795–801.

11. Breast Cancer Now. The cost of breast cancer: Modelling the economic impact to the UK [Internet]. 2024 [cited 2024 Feb 16]. Available from: https://demos.co.uk/wp-content/uploads/2024/01/Cost-of-Breast-Cancer-Report.pdf

12. Curigliano G, Castelo-Branco L, Gennari A, Harbeck N, Criscitiello C. ESMO Metastatic Breast Cancer Living Guideline > ER-positive HER2-negative Breast Cancer. 2023 May [cited 2023 Aug 11]; Available from: https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline/er-positive-her2-negative-breast-cancer

13. Cogliati V, Capici S, Pepe FF, di Mauro P, Riva F, Cicchiello F, et al. How to Treat HR+/HER2- Metastatic Breast Cancer Patients after CDK4/6 Inhibitors: An Unfinished Story. Life Basel Switz. 2022 Mar 5;12(3):378.

14. Chen YC, Yu J, Metcalfe C, De Bruyn T, Gelzleichter T, Malhi V, et al. Latest generation estrogen receptor degraders for the treatment of hormone receptor-positive breast cancer. Expert Opin Investig Drugs. 2022 Jun;31(6):515–29.

15. Jhaveri KL, Jeselsohn R, Ma CX, Lim E, Yonemori K, Harnden K, et al. Imlunestrant, with or without everolimus or alpelisib, in ER+, HER2- advanced breast cancer (aBC): Results from the phase 1a/b EMBER study.

16. Lin NU, Borges VF, Patel MR, Okera M, Meisel J, Wesolowski R, et al. Results from the phase 1/2 study of OP-1250, an oral complete estrogen receptor (ER) antagonist (CERAN) and selective ER degrader (SERD) in patients (pts) with advanced or metastatic ER-positive, HER2-negative breast cancer. Ann Oncol. 34(S2):S338.

17. Kalinsky K, Accordino MK, Chiuzan C, Mundi PS, Sakach E, Sathe C, et al. Randomized Phase II Trial of Endocrine Therapy With or Without Ribociclib After Progression on Cyclin-Dependent Kinase 4/6 Inhibition in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer: MAINTAIN Trial. J Clin Oncol Off J Am Soc Clin Oncol. 2023 Aug 20;41(24):4004–13.

18. Turner NC, Swift C, Kilburn L, Fribbens C, Beaney M, Garcia-Murillas I, et al. *ESR1* Mutations and Overall Survival on Fulvestrant versus Exemestane in Advanced Hormone Receptor-Positive Breast Cancer: A Combined Analysis of the Phase III SoFEA and EFECT Trials. Clin Cancer Res Off J Am Assoc Cancer Res. 2020 Oct 1;26(19):5172–7.

19. NICE. Everolimus with exemestane for treating advanced breast cancer after endocrine therapy: TA421 [Internet]. National Institute for Health and Care Excellence; 2016 Dec [cited 2023 Aug 11]. Available from: https://www.nice.org.uk/guidance/ta421

20. NICE. Alpelisib with fulvestrant for treating hormone receptor-positive, HER2-negative, *PIK3CA*-mutated advanced breast cancer: TA816 [Internet]. National Institute for Health and Care Excellence; 2022 Aug [cited 2023 Aug 11]. Available from: https://www.nice.org.uk/guidance/ta816

21. Novartis. Alpelisib (PIQRAY): full prescribing information [Internet]. 2022 [cited 2023 Aug 11]. Available from: https://www.novartis.com/us-en/sites/novartis_us/files/piqray.pdf

22. Baselga J, Campone M, Piccart M, Burris HA, Rugo HS, Sahmoud T, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med. 2012 Feb 9;366(6):520–9.

23. Rugo HS, Pritchard KI, Gnant M, Noguchi S, Piccart M, Hortobagyi G, et al. Incidence and time course of everolimus-related adverse events in postmenopausal women with hormone receptor-positive advanced breast cancer: insights from BOLERO-2. Ann Oncol. 2014 Apr;25(4):808–15.

24. Novartis. Everolimus (AFINITOR): full prescribing information [Internet]. 2022 [cited 2023 Aug 11]. Available from: https://www.novartis.com/us-en/sites/novartis_us/files/afinitor.pdf

25. André F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS, et al. Alpelisib for *PIK3CA*-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2019 May 16;380(20):1929–40.

26. AstraZeneca. Fulvestrant (FASLODEX): full prescribing information [Internet]. 2011 [cited 2023 Aug 11]. Available from: https://medicalinformation.astrazeneca-us.com/home/prescribing-information/faslodex.html

27. MHRA. Summary of Product Characteristics (KORSERDU) [Internet]. Medicines and Healthcare products Regulatory Agency; 2023 Dec [cited 2024 Jan 22]. Available from: https://mhraproducts4853.blob.core.windows.net/docs/95258a8afaced7089a5b5cbdc45108ce15ac7bf2

28. Bardia A. PS17-02 Elacestrant vs standard-of-care in ER+/HER2- advanced or metastatic breast cancer (mBC) with *ESR1* mutation: key biomarkers and clinical subgroup analyses from the phase 3 EMERALD trial. SABCS. 2023 Dec 8;

29. Menarini Stemline. UK Clinical Expert Opinion, Data on File. 2024.

30. Bardia A, Bidard FC, Neven P, Streich G, Montero AJ, Forget F, et al. Abstract GS3-01: GS3-01 EMERALD phase 3 trial of elacestrant versus standard of care endocrine therapy in patients with ER+/HER2- metastatic breast cancer: Updated results by duration of prior CDK4/6i in metastatic setting. Cancer Res. 2023 Mar 1;83(5_Supplement):GS3-01.

31. NICE. Final scope: Elacestrant for treating oestrogen receptor-positive, HER2-negative advanced breast cancer with an *ESR1* mutation after at least 1 endocrine treatment [ID6225]. [Internet]. National Institute for Health and Care Excellence; 2024 Feb [cited 2024 Feb 13]. Available from: https://www.nice.org.uk/guidance/gid-ta11263/documents/final-scope

32. Bardia A, Aftimos P, Bihani T, Anderson-Villaluz AT, Jung J, Conlan MG, et al. EMERALD: Phase III trial of elacestrant (RAD1901) vs endocrine therapy for previously treated ER+ advanced breast cancer. Future Oncol. 2019 Oct;15(28):3209–18.

33. Bidard FC, Kaklamani VG, Neven P, Streich G, Montero AJ, Forget F, et al. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. J Clin Oncol Off J Am Soc Clin Oncol. 2022 Oct 1;40(28):3246–56.

34. Menarini Stemline. ORSERDU (elacestrant) - prescribing information [Internet]. [cited 2023 Aug 10]. Available from: https://rxmenarinistemline.com/ORSERDU_elacestrant_Full_Prescribing_Information.pdf

35. Cancer Research UK. What is breast cancer? [Internet]. [cited 2023 Aug 10]. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/about

36. Cancer Research UK. Incidence (2020) and Survival of Cancer Cases by Known Stage at Diagnosis, Breast Cancer, England [Internet]. [cited 2023 Aug 11]. Available from: https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/

37. Breast Cancer Now. Breast cancer facts and statistics [Internet]. 2024 [cited 2024 Feb 21]. Available from: https://breastcancernow.org/about-us/why-we-do-it/breast-cancer-facts-and-statistics/#diagnosis-statistics

38. Aebi S, Karlsson P, Wapnir IL. Locally advanced breast cancer. Breast Off J Eur Soc Mastology. 2021 Dec 15;62(Suppl 1):S58–62.

39. VanderWalde A, Hurria A. Early breast cancer in the older woman. Clin Geriatr Med. 2012 Feb;28(1):10.1016/j.cger.2011.10.002.

40. Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro MS, André F, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020 Dec 1;31(12):1623–49.

41. Cardoso F, Costa A, Norton L, Senkus E, Aapro M, André F, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Breast Edinb Scotl. 2014 Oct;23(5):489–502.

42. Cancer Research UK. Proportion of Cancer Cases by Stage at Diagnosis [Internet]. [cited 2023 Aug 11]. Available from: https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/

43. Dewis R, Gribbin J. Breast Cancer: Diagnosis and Treatment: An Assessment of Need. In: Breast Cancer: Diagnosis and Treatment: An Assessment of Need [Internet]. National Collaborating Centre for Cancer (UK); 2009 [cited 2023 Aug 31]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK61914/

44. Bidard FC, Hardy-Bessard AC, Dalenc F, Bachelot T, Pierga JY, de la Motte Rouge T, et al. Switch to fulvestrant and palbociclib versus no switch in advanced breast cancer with rising *ESR1* mutation during aromatase inhibitor and palbociclib therapy (PADA-1): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol. 2022 Nov;23(11):1367–77.

45. Im SA, Lu YS, Bardia A, Harbeck N, Colleoni M, Franke F, et al. Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer. N Engl J Med. 2019 Jul 25;381(4):307–16.

46. Goetz MP, Toi M, Campone M, Sohn J, Paluch-Shimon S, Huober J, et al. MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2017 Nov 10;35(32):3638–46.

47. Brett JO, Spring LM, Bardia A, Wander SA. *ESR1* mutation as an emerging clinical biomarker in metastatic hormone receptor-positive breast cancer. Breast Cancer Res BCR. 2021 Aug 15;23(1):85.

48. Jeselsohn R, Yelensky R, Buchwalter G, Frampton G, Meric-Bernstam F, Gonzalez-Angulo AM, et al. Emergence of constitutively active estrogen receptor-α mutations in pretreated advanced estrogen receptor positive breast cancer. Clin Cancer Res Off J Am Assoc Cancer Res. 2014 Apr 1;20(7):1757–67.

49. Chaudhary N, Chibly AM, Collier A, Martinalbo J, Perez-Moreno P, Moore HM, et al. CDK4/6i-treated HR+/HER2- breast cancer tumors show higher *ESR1* mutation prevalence and more altered genomic landscape. Npj Breast Cancer. 2024 Feb 22;10(1):1–12.

50. Reinert T, Saad ED, Barrios CH, Bines J. Clinical Implications of *ESR1* Mutations in Hormone Receptor-Positive Advanced Breast Cancer. Front Oncol. 2017 Mar 15;7:26.

51. Mittal A, Molto Valiente C, Tamimi F, Schlam I, Sammons S, Tolaney SM, et al. Filling the Gap after CDK4/6 Inhibitors: Novel Endocrine and Biologic Treatment Options for Metastatic Hormone Receptor Positive Breast Cancer. Cancers. 2023 Mar 28;15(7):2015.

52. Chandarlapaty S, Chen D, He W, Sung P, Samoila A, You D, et al. Prevalence of *ESR1* Mutations in Cell-Free DNA and Outcomes in Metastatic Breast Cancer: A Secondary Analysis of the BOLERO-2 Clinical Trial. JAMA Oncol. 2016 Oct 1;2(10):1310–5.

53. Clatot F, Perdrix A, Augusto L, Beaussire L, Delacour J, Calbrix C, et al. Kinetics, prognostic and predictive values of *ESR1* circulating mutations in metastatic breast cancer patients progressing on aromatase inhibitor. Oncotarget. 2016 Nov 15;7(46):74448–59.

54. Turner N, Rugo HS, Ciruelos EM, Ruiz-Borrego M, Drullinsky P, Lerebours F, et al. Abstract PD15-01: Impact of *ESR1* mutations on endocrine therapy (ET) plus alpelisib benefit in patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), *PIK3CA*-mutated, advanced breast cancer (ABC) who progressed on or after prior cyclin-dependent kinase inhibitor (CDK4/6i) therapy in the BYLieve trial. Cancer Res. 2022 Feb 15;82(4_Supplement):PD15-01.

55. Hurvitz SA, Clark AS, Rugo HS, Bardia A, Zelnak A, Yardley DA, et al. Abstract PD13-03: Ribociclib, everolimus, exemestane triplet therapy in HR+/HER2− advanced breast cancer after progression on a CDK4/6 inhibitor: Final efficacy, safety, and biomarker results from TRINITI-1. Cancer Res. 2022 Feb 15;82(4_Supplement):PD13-03.

56. Cancer Research UK. Breast cancer incidence (invasive statistics) [Internet]. [cited 2024 Apr 12]. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive#heading-Zero

57. Koo MM, von Wagner C, Abel GA, McPhail S, Rubin GP, Lyratzopoulos G. Typical and atypical presenting symptoms of breast cancer and their associations with diagnostic intervals: Evidence from a national audit of cancer diagnosis. Cancer Epidemiol. 2017 Jun;48:140–6.

58. Cancer Research UK. Symptoms of breast cancer [Internet]. [cited 2024 Apr 12]. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/symptoms

59. Breast Cancer Now. Secondary breast cancer treatment [Internet]. [cited 2024 Apr 12]. Available from: https://breastcancernow.org/information-support/facing-breast-cancer/secondary-metastatic-breast-cancer/secondary-breast-cancer-treatment#Aim%20of%20treatment

60. Walker MS, Hasan M, Mi Yim Y, Yu E, Stepanski EJ, Schwartzberg LS. Retrospective study of the effect of disease progression on patient reported outcomes in HER-2 negative metastatic breast cancer patients. Health Qual Life Outcomes. 2011 Jun 20;9:46.

61. Davie A, Carter GC, Rider A, Pike J, Lewis K, Bailey A, et al. Real-world patient-reported outcomes of women receiving initial endocrine-based therapy for HR+/HER2− advanced breast cancer in five European countries. BMC Cancer. 2020 Sep 7;20(1):855.

62. Flood E, Krasnow A, Orbegoso C, Karantzoulis S, Bailey J, Bayet S, et al. Using qualitative interviews to identify patient-reported clinical trial endpoints and analyses that are the most meaningful to patients with advanced breast cancer. PLOS ONE. 2023 Jan 17;18(1):e0280259.

63. Cardoso F, Rihani J, Harmer V, Harbeck N, Casas A, Rugo HS, et al. Quality of Life and Treatment-Related Side Effects in Patients With HR+/HER2- Advanced Breast Cancer: Findings From a Multicountry Survey. The Oncologist. 2023 Oct 3;28(10):856–65.

64. Fallowfield L, Starkings R, Palmieri C, Tait A, Stephen L, May S, et al. Living with metastatic breast cancer (LIMBER): experiences, quality of life, gaps in information, care and support of patients in the UK. Support Care Cancer. 2023;31(8):459.

65. Meegdes M, Geurts SME, Erdkamp FLG, Dercksen MW, Vriens BEPJ, Aaldering KNA, et al. Real-world time trends in overall survival, treatments and patient characteristics in HR+/HER2- metastatic breast cancer: an observational study of the SONABRE Registry. Lancet Reg Health Eur. 2023 Mar;26:100573.

66. Yin W, Horblyuk R, Perkins JJ, Sison S, Smith G, Snider JT, et al. Association Between Breast Cancer Disease Progression and Workplace Productivity in the United States. J Occup Environ Med. 2017 Feb;59(2):198.

67. İzci F, İlgün AS, Fındıklı E, Özmen V. Psychiatric Symptoms and Psychosocial Problems in Patients with Breast Cancer. J Breast Health. 2016 Jul 1;12(3):94–101.

68. Reich M, Lesur A, Perdrizet-Chevallier C. Depression, quality of life and breast cancer: a review of the literature. Breast Cancer Res Treat. 2008 Jul;110(1):9–17.

69. Breast Cancer Now. Global Status of Advanced/Metastatic Breast Cancer 2005-2015 Decade Report [Internet]. [cited 2024 Feb 16]. Available from: https://breastcancernow.org/sites/default/files/global_status_of_metastatic_breast_cancer_2005_to_2015_decade_report_summary.pdf

70. Kawahara T, Taira N, Shiroiwa T, Hagiwara Y, Fukuda T, Uemura Y, et al. Minimal important differences of EORTC QLQ-C30 for metastatic breast cancer patients: Results from a randomized clinical trial. Qual Life Res Int J Qual Life Asp Treat Care Rehabil. 2022 Jun;31(6):1829–36.

71. American Cancer Society. Chemotherapy for Breast Cancer [Internet]. [cited 2023 Aug 10]. Available from: https://www.cancer.org/cancer/types/breast-cancer/treatment/chemotherapy-for-breast-cancer.html

72. Ream E, Richardson A, Lucas G, Marcu A, Foster R, Fuller G, et al. Understanding the support needs of family members of people undergoing chemotherapy: A longitudinal qualitative study. Eur J Oncol Nurs. 2021 Feb 1;50:101861.

73. Mitra D, Wood R, Courcy JD, Iyer S. Patient Reported Health Utility in HR+/HER2-Advanced/Metastatic Breast Cancer. Value Health. 2016 Nov 1;19(7):A749.

74. Wallwiener M, Simoes E, Sokolov AN, Brucker SY, Fasching PA, Graf J. Health-related Quality of Life in Metastatic and Adjuvant Breast Cancer Patients. Geburtshilfe Frauenheilkd. 2016 Oct;76(10):1065–73.

75. Brady MJ, Cella DF, Mo F, Bonomi AE, Tulsky DS, Lloyd SR, et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. J Clin Oncol Off J Am Soc Clin Oncol. 1997 Mar;15(3):974–86.

76. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. Br J Cancer. 2006 Sep 18;95(6):683–90.

77. Gennari A, André F, Barrios CH, Cortés J, Azambuja E de, DeMichele A, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer☆. Ann Oncol. 2021 Dec 1;32(12):1475–95.

78. NICE. Early and locally advanced breast cancer: diagnosis and management NG101 [Internet]. National Institute for Health and Care Excellence; 2023 Jun [cited 2023 Aug 10]. Available from: https://www.nice.org.uk/guidance/ng101/resources/early-and-locally-advanced-breast-cancer-diagnosis-and-management-pdf-66141532913605

79. NICE. Advanced breast cancer: diagnosis and treatment CG81 [Internet]. National Institute for Health and Care Excellence; 2017 Aug [cited 2023 Aug 10]. Available from: https://www.nice.org.uk/guidance/cg81/resources/advanced-breast-cancer-diagnosis-and-treatment-pdf-975683850181

80. NICE. 2023 surveillance of early and locally advanced breast cancer: diagnosis and management (NICE guideline NG101) and advanced breast cancer: diagnosis and treatment (NICE guideline CG81) [Internet]. [cited 2024 Mar 6]. Available from: https://www.nice.org.uk/guidance/ng101/resources/2023-surveillance-of-early-and-locally-advanced-breast-cancer-diagnosis-and-management-nice-guideline-ng101-and-advanced-breast-cancer-diagnosis-and-treatment-nice-guideline-cg81-pdf-14672057094853#:~:text=Recommendation%201.1.,of%20breast%20or%20ovarian%20cancer.

81. NICE. Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer: TA495. National Institute for Health and Care Excellence; 2017 Dec.

82. NICE. Ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer: TA496 [Internet]. National Institute for Health and Care Excellence; 2017 Dec [cited 2023 Aug 11]. Available from: https://www.nice.org.uk/guidance/ta496

83. NICE. Abemaciclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer: TA563 [Internet]. National Institute for Health and Care Excellence; 2019 Feb [cited 2023 Aug 11]. Available from: https://www.nice.org.uk/guidance/ta563

84. NICE. Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy: TA836 [Internet]. National Institute for Health and Care Excellence; 2022 Oct [cited 2023 Aug 11]. Available from: https://www.nice.org.uk/guidance/ta836

85. NICE. Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy: TA725 [Internet]. National

Institute for Health and Care Excellence; 2021 Sep [cited 2023 Aug 11]. Available from: https://www.nice.org.uk/guidance/ta725

86. NICE. Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy: TA687 [Internet]. National Institute for Health and Care Excellence; 2021 Mar [cited 2023 Aug 11]. Available from: https://www.nice.org.uk/guidance/ta687

87. NICE. Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens: TA423 [Internet]. National Institute for Health and Care Excellence; 2016 Dec [cited 2023 Aug 17]. Available from: https://www.nice.org.uk/guidance/ta423

88. NICE. Gemcitabine for the treatment of metastatic breast cancer: TA116 [Internet]. National Institute for Health and Care Excellence; 2007 Jan [cited 2023 Aug 17]. Available from: https://www.nice.org.uk/guidance/ta116

89. Gagan J, Van Allen EM. Next-generation sequencing to guide cancer therapy. Genome Med. 2015 Jul 29;7(1):80.

90. Takeshita T, Yamamoto Y, Yamamoto-Ibusuki M, Tomiguchi M, Sueta A, Murakami K, et al. Comparison of *ESR1* Mutations in Tumor Tissue and Matched Plasma Samples from Metastatic Breast Cancer Patients. Transl Oncol. 2017 Oct 1;10(5):766–71.

91. Vidula N, Niemierko A, Malvarosa G, Yuen M, Lennerz J, Iafrate AJ, et al. Tumor Tissue- versus Plasma-based Genotyping for Selection of Matched Therapy and Impact on Clinical Outcomes in Patients with Metastatic Breast Cancer. Clin Cancer Res. 2021 Jun 15;27(12):3404–13.

92. NHS England. NHS England » National genomic test directory [Internet]. [cited 2023 Aug 10]. Available from: https://www.england.nhs.uk/publication/national-genomic-test-directories/

93. EMA. Piqray - Summary of Produce Characteristics (SmPC) [Internet]. [cited 2024 Mar 20]. Available from: https://www.ema.europa.eu/en/documents/product-information/piqray-epar-product-information_en.pdf

94. Fallowfield L, Atkins L, Catt S, Cox A, Coxon C, Langridge C, et al. Patients' preference for administration of endocrine treatments by injection or tablets: results from a study of women with breast cancer. Ann Oncol Off J Eur Soc Med Oncol. 2006 Feb;17(2):205–10.

95. Bihani T, Patel HK, Arlt H, Tao N, Jiang H, Brown JL, et al. Elacestrant (RAD1901), a Selective Estrogen Receptor Degrader (SERD), Has Antitumor Activity in Multiple ER+ Breast Cancer Patient-derived Xenograft Models. Clin Cancer Res Off J Am Assoc Cancer Res. 2017 Aug 15;23(16):4793–804.

96. Garner F, Shomali M, Paquin D, Lyttle CR, Hattersley G. RAD1901: a novel, orally bioavailable selective estrogen receptor degrader that demonstrates antitumor activity in breast cancer xenograft models. Anticancer Drugs. 2015 Oct;26(9):948–56.

97. Patel HK, Tao N, Lee KM, Huerta M, Arlt H, Mullarkey T, et al. Elacestrant (RAD1901) exhibits anti-tumor activity in multiple ER+ breast cancer models resistant to CDK4/6 inhibitors. Breast Cancer Res BCR. 2019 Dec 18;21(1):146.

98. Menarini Stemline. Clinical Study Report v.2: Elacestrant monotherapy vs. standard of care for the treatment of patients with ER+/HER2- advanced breast cancer following CDK4/6 inhibitor therapy: A phase 3 randomized, open-label, active-controlled, multicenter trial (EMERALD). 2023 Jan p. 4424.

99. Bidard FC, Kaklamani VG, Neven P, Streich G, Montero AJ, Forget F, et al. Supplementary Appendix - Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. J Clin Oncol Off J Am Soc Clin Oncol. 2022 Oct 1;40(28):3246–56.

100. Menarini Stemline. EMERALD Data on File: UK Requests, CDK4/6 12 month plus data for *ESR1* mutation population.

101. Menarini Stemline. EMERALD Data on File: UK Requests, CDK4/6 12 month plus data for dual mutation population (*ESR1* + *PIK3CA*).

102. Menarini Stemline. Overall Survival Addendum to Clinical Study Report v.2 RAD1901-308 | Elacestrant monotherapy vs. standard of care for the treatment of patients with ER+/HER2- advanced breast cancer following CDK4/6 inhibitor therapy: a Phase 3 randomized, open-label, active-controlled, multicenter trial (EMERALD) | overall survival addendum as of 2nd September 2022. 2023 Oct p. 14.

103. Dubash TD, Bardia A, Chirn B, Reeves BA, LiCausi JA, Burr R, et al. Modeling the novel SERD elacestrant in cultured fulvestrant-refractory HR-positive breast circulating tumor cells. Breast Cancer Res Treat. 2023 Aug;201(1):43–56.

104. Aftimos PG, Cortés J, Bidard FC, V. Kaklamani, Bardia A, Neven P, et al. 220P Elacestrant vs fulvestrant or aromatase inhibitor (AI) in phase III trial evaluating elacestrant, an oral selective estrogen receptor degrader (SERD), vs standard of care (SOC) endocrine monotherapy for ER+/HER2- advanced/metastatic breast cancer (mBC): Subgroup analysis from EMERALD. Ann Oncol. 2022 Sep 1;33:S638.

105. Cortés J. AB363 − EMERALD trial analysis of Patient-reported outcomes (PROs) in patients with ER+/HER2− advanced or metastatic breast cancer (mBC) Comparing oral elacestrant vs standard of care (SOC) endocrine therapy. IFODS.

106. Rugo HS, Neven P, Saffie I, Park YH, De Laurentiis M, Lerebours F, et al. Abstract PD13-05: Alpelisib + fulvestrant in patients with *PIK3CA*-mutated, HR+, HER2— advanced breast cancer (ABC) who received chemotherapy or endocrine therapy (ET) as immediate prior treatment: BYLieve Cohort C primary results and exploratory biomarker analyses. Cancer Res. 2022 Feb 15;82(4_Supplement):PD13-05.

107. Raphael A, Salmon-Divon M, Epstein J, Zahavi T, Sonnenblick A, Shachar SS. Alpelisib Efficacy in Hormone Receptor-Positive HER2-Negative *PIK3CA*-Mutant Advanced Breast Cancer Post-Everolimus Treatment. Genes. 2022 Sep 29;13(10).

108. Menarini Stemline. Statistical Analysis Plan RAD1901-308. 2021 Mar p. 65.

109. Cortés J, Bidard FC, Bardia A, Kaklamani VG, Vlachaki I, Tonini G, et al. 188O EMERALD trial analysis of patient-reported outcomes (PROs) in patients with ER+/HER2− advanced or metastatic breast cancer (mBC) comparing oral elacestrant vs standard of care (SOC) endocrine therapy. ESMO Open. 2023 May;8(1):101377.

110. Menarini Stemline. Clinical Study Protocol (RAD1901-308) | Elacestrant monotherapy vs. standard of care for the treatment of patients with ER+/HER2- advanced breast cancer following CDK4/6 inhibitor therapy: a Phase 3 randomized, open-label, active-controlled, multicentre trial (EMERALD). 2020 Mar p. 118.

111. Study Record | ClinicalTrials.gov [Internet]. [cited 2023 Aug 11]. Available from: https://clinicaltrials.gov/study/NCT03778931

112. Lindeman GJ, Fernando TM, Bowen R, Jerzak KJ, Song X, Decker T, et al. VERONICA: Randomized Phase II Study of Fulvestrant and Venetoclax in ER-Positive Metastatic Breast Cancer Post-CDK4/6 Inhibitors - Efficacy, Safety, and Biomarker Results. Clin Cancer Res Off J Am Assoc Cancer Res. 2022 Aug 2;28(15):3256–67.

113. NICE. Single technology appraisal and highly specialised technologies evaluation: User guide for company evidence submission template [Internet]. [cited 2024 Feb 2]. Available from: https://www.nice.org.uk/process/pmg24/resources/single-technology-appraisal-and-highly-specialised-technologies-evaluation-user-guide-for-company-evidence-submission-template-pdf-72286715419333

114. European Medicines Agency. Assessment report: Orserdu. International non-proprietary name: elacestrant. Procedure No. EMEA/H/C/005898/0000. Report No.: EMA/CHMP/358130/2023.

115. Menarini Stemline. EMERALD Data on File: UK Requests, additional all patients with *ESR1*-mut PRO data.

116. Hamilton EP, Dees EC, Wang JSZ, Kim A, Korpal M, Rimkunas V, et al. Phase I dose escalation of H3B-6545, a first-in-class highly Selective ERα Covalent Antagonist (SERCA), in women with ER-positive, HER2-negative breast cancer (HR+ BC). J Clin Oncol. 2019 May 20;37(15_suppl):1059–1059.

117. Hamilton EP, Oliveira M, Banerji U, Hernando C, Garcia-Corbacho J, Armstrong A, et al. A phase I dose escalation and expansion study of the next generation oral SERD AZD9833 in women with ER-positive, HER2-negative advanced breast cancer. J Clin Oncol. 2020 May 20;38(15_suppl):1024–1024.

118. Lim E, Jhaveri KL, Perez-Fidalgo JA, Bellet M, Boni V, Perez Garcia JM, et al. A phase Ib study to evaluate the oral selective estrogen receptor degrader GDC-9545 alone or combined with palbociclib in metastatic ER-positive HER2-negative breast cancer. J Clin Oncol. 2020 May 20;38(15_suppl):1023–1023.

119. NICE. Introduction to health technology evaluation | NICE health technology evaluations: the manual | Guidance | NICE [Internet]. NICE; 2022 [cited 2024 Mar 20]. Available from: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation

120. NICE. BNF: British National Formulary - NICE [Internet]. NICE; [cited 2021 Jan 29]. Available from: https://bnf.nice.org.uk/drugs/

121. eMIT. Drugs and pharmaceutical electronic market information tool (eMIT) [Internet]. GOV.UK. 2023 [cited 2024 Mar 20]. Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit

122. NHS. National Cost Collection for the NHS [Internet]. 2022 [cited 2024 Jan 9]. Available from: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/

123. PSSRU. Unit Costs of Health and Social Care [Internet]. 2022 [cited 2024 Mar 20]. Available from: https://kar.kent.ac.uk/100519/1/Unit%20Costs%20of%20health%20and%20Social%20Care%202022%20%28amended%2013%20July%202023%29.pdf

124. Latimer NR. NICE DSU Technical Support Document 14. Med Decis Making. 2013 Aug;33(6):743–54.

125. Hernandez M, Pudney S. eq5dmap: A command for mapping between EQ-5D-3L and EQ-5D-5L. Stata J. 2017 Dec 3;18.

126. Swinburn P, Lloyd A, Nathan P, Choueiri TK, Cella D, Neary MP. Elicitation of health state utilities in metastatic renal cell carcinoma. Curr Med Res Opin. 2010 May;26(5):1091–6.

127. Telford C, Bertranou E, Large S, Phelps H, Ekman M, Livings C. Cost-Effectiveness Analysis of Fulvestrant 500 mg in Endocrine Therapy-Naïve Postmenopausal Women with Hormone Receptor-Positive Advanced Breast Cancer in the UK. PharmacoEconomics Open. 2019 Apr 25;3(4):559–70.

128. Hagiwara Y, Shiroiwa T, Shimozuma K, Kawahara T, Uemura Y, Watanabe T, et al. Impact of Adverse Events on Health Utility and Health-Related Quality of Life in Patients Receiving First-Line Chemotherapy for Metastatic Breast Cancer: Results from the SELECT BC Study. PharmacoEconomics. 2018 Feb;36(2):215–23.

129. Smith-Palmer J, Bae JP, Boye KS, Norrbacka K, Hunt B, Valentine WJ. Evaluating health-related quality of life in type 1 diabetes: a systematic literature review of utilities for adults with type 1 diabetes. Clin Outcomes Res CEOR. 2016;8:559–71.

130. Mistry R, May JR, Suri G, Young K, Brixner D, Oderda G, et al. Cost-Effectiveness of Ribociclib plus Letrozole Versus Palbociclib plus Letrozole and Letrozole Monotherapy in the First-Line Treatment of Postmenopausal Women with HR+/HER2- Advanced or Metastatic Breast Cancer: A U.S. Payer Perspective. J Manag Care Spec Pharm. 2018 Jun;24(6):514–23.

131. Martí SG, Colantonio L, Bardach A, Galante J, Lopez A, Caporale J, et al. A cost-effectiveness analysis of a 10-valent pneumococcal conjugate vaccine in children in six Latin American countries. Cost Eff Resour Alloc CE. 2013 Aug 30;11(1):21.

132. Paracha N, Abdulla A, MacGilchrist KS. Systematic review of health state utility values in metastatic non-small cell lung cancer with a focus on previously treated patients. Health Qual Life Outcomes. 2018 Sep 12;16(1):179.

133. Tolley K, Goad C, Yi Y, Maroudas P, Haiderali A, Thompson G. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. Eur J Health Econ HEPAC Health Econ Prev Care. 2013 Oct;14(5):749–59.

134. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health. 20100310th ed. 2010 Aug;13(5):509–18.

135. Medicinal forms | Everolimus | Drugs | BNF content published by NICE [Internet]. [cited 2024 Mar 20]. Available from: https://bnf.nice.org.uk/drugs/everolimus/medicinal-forms/

136. Alpelisib [Specialist drug] | Drugs | BNF content published by NICE [Internet]. [cited 2024 Mar 20]. Available from: https://bnf.nice.org.uk/drugs/alpelisib-specialist-drug/

137. EMA. Afinitor - Summary of Produce Characteristics (SmPC) [Internet]. [cited 2024 Mar 20]. Available from: https://www.ema.europa.eu/en/documents/product-information/afinitor-epar-product-information_en.pdf

138. EMC. EXEMESTANE 25 mg Coated tablets - Summary of Product Characteristics (SmPC) [Internet]. [cited 2024 Mar 20]. Available from: https://www.medicines.org.uk/emc/product/3937/smpc/print

139. Jerusalem G, Mariani G, Ciruelos EM, Martin M, Tjan-Heijnen VCG, Neven P, et al. Safety of everolimus plus exemestane in patients with hormone-receptor-positive, HER2-negative locally advanced or metastatic breast cancer progressing on prior non-steroidal aromatase inhibitors: primary results of a phase IIIb, open-label, single-arm, expanded-access multicenter trial (BALLET). Ann Oncol Off J Eur Soc Med Oncol. 2016 Sep;27(9):1719–25.

140. Alaklabi S, Roy AM, Attwood K, George A, O'Connor T, Early A, et al. Real world outcomes with alpelisib in metastatic hormone receptor-positive breast cancer patients: A single institution experience. Front Oncol. 2022;12:1012391.

141. NICE. Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer (Review of TA619): TA836 [Internet]. 2022 Mar [cited 2024 Apr 18]. Available from: https://www.nice.org.uk/guidance/ta836/documents/committee-papers-2

142. London Cancer Alliance. Breast Pathway Group - Capecitabine in Advanced Breast Cancer [Internet]. 2014 [cited 2024 Mar 20]. Available from: https://rmpartners.nhs.uk/wp-content/uploads/2017/03/LCA-Breast-capecitabine-ABC-November-2014.pdf

143. EMA. Summary of Product Characteristics (Xeloda) [Internet]. [cited 2024 Apr 3]. Available from: https://www.ema.europa.eu/en/documents/product-information/xeloda-epar-product-information_en.pdf

144. Dieras V, Chevallier B, Kerbrat P, Krakowski I, Roche H, Misset JL, et al. A multicentre phase II study of docetaxel 75 mg m^2 as first-line chemotherapy for patients with advanced breast cancer: report of the Clinical Screening Group of the EORTC. European Organization for Research and Treatment of Cancer. Br J Cancer. 1996 Aug;74(4):650–6.

145. EMA. Abraxane - Summary of Produce Characteristics (SmPC) [Internet]. [cited 2024 Mar 21]. Available from: https://www.ema.europa.eu/en/documents/product-information/abraxane-epar-product-information_en.pdf

146. Round J, Jones L, Morris S. Estimating the cost of caring for people with cancer at the end of life: A modelling study. Palliat Med. 2015 Dec;29(10):899–907.

147. PSSRU. V. Sources of Information [Internet]. 2021 [cited 2024 Mar 20]. Available from: https://www.pssru.ac.uk/pub/uc/uc2021/sourcesofinformation.pdf

148. Schneider P, McNamara S, Love-Koh J, Doran T, Gutacker N. QALY Shortfall Calculator [Internet]. [cited 2024 Mar 21]. Available from: https://shiny.york.ac.uk/shortfall

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Elacestrant for treating oestrogen receptor-positive, HER2-negative advanced breast cancer with an *ESR1* mutation after at least 1 endocrine treatment [ID6225]

Summary of Information for Patients (SIP)

May 2024

File name	Version	Contains confidential information	Date
ID6225_Elacestrant-ESR1-mutated-aBC_SIP UPLOADED_(NO CON)	3.0	No	13TH May 2024

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company that is seeking approval from NICE for their treatment to be sold to the NHS for use in England and Wales. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the Public Involvement team at NICE will have read it to double-check there is no marketing or promotional content before it is sent to you.

The **SIP** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article.

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic: Elacestrant dihydrochloride Brand name: KORSERDU®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Elacestrant is intended to be used as a treatment for postmenopausal women, and men, with oestrogen receptor-positive (ER+)/human epidermal factor receptor 2-negative (HER2-), advanced/metastatic breast cancer (mBC) with an activating oestrogen receptor 1 (*ESR1)* mutation (*ESR1-mut)* who have disease progression following at least (≥)12 months of prior treatment with endocrine therapy (ET) + a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i). This subpopulation is smaller than the potential population covered by the marketing authorisation,[1] as this is where clinicians believe it will provide most value in practice in the UK.[2–4] Elacestrant will be used to treat patients who would otherwise be suitable for treatment with everolimus + exemestane or, if they have both a mutation in phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA)* and *ESR1* (*PIK3CA-mut* + *ESR1-mut,* dual mutated), with alpelisib + fulvestrant. Please see Section 2a for more information on this disease and descriptors for this population.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Elacestrant monotherapy was granted a UK marketing authorisation by the Medicines and Healthcare Products Regulatory Agency (MHRA) on 6 December 2023 and is indicated for the treatment of postmenopausal women, and men, with ER+/HER2-, locally advanced/mBC with an activating *ESR1-mut* who have disease progression following at least one line of ET including a CDK4/6i (see link here for full document).[1]

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Sponsored UK Interdisciplinary Breast Cancer Symposium (UKIBCS) 2024 which is hosted by Breast Cancer Now (£12,500 inc. VAT): To support the work of the organising committee in providing those with an interest in breast cancer the opportunity to convene and discuss the latest advances in the field and what this means for clinical practice, across the disciplines, within UK breast cancer care.

The Company is planning to sponsor the Secondary Breast Cancer Patient Summit (9 to 11 July 2024): To support the UK mBC patient community in having their voices heard within a forum designed specifically for them, and by them.

The Company is planning to sponsor the Breast Cancer Now's healthcare professional (HCP) Network (Nursing Conference June 2024): To support the first event in a series of HCP conferences from Breast Cancer Now, designed to improve support for HCPs and outcomes for patients.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England. Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained

ER+/HER2- advanced/mBC

Breast cancer (BC) is the leading cause of cancer in women and the fourth leading cause of cancer deaths in the UK.[5] The disease occurs when abnormal cells in parts of the breast grow and divide uncontrollably, forming a mass.[6]

Advanced BC refers to both locally advanced BC, also known as Stage 3 BC that cannot be removed by surgery (when cancer has spread beyond the breast to lymph nodes close to the breast, to the skin of the chest, or to the chest wall), and metastatic BC, also known as secondary or stage 4 BC (where the cancer has spread beyond the breast to other parts of the body such as the bones, brain, liver and lungs).[7, 8]

Approximately 35% of people with early or locally advanced BC that can be removed by surgery will progress to mBC within 10 years of diagnosis, and approximately 13% of people with BC will have advanced/mBC at diagnosis.[9, 10]

BCs are broken down into different subtypes based on the presence (+) or absence (-) of proteins in or on the cancer cell such as oestrogen receptors (ER), progesterone receptors (PR) and human epidermal growth factor receptor 2 (HER2). Tumours expressing ER and/or PR are considered hormone receptor-positive breast cancers (HR+). The most common subtype of BC is ER+/HER2-, accounting for approximately 70% of cases,[11] and is driven by oestrogen produced in the body.

Development of *ESR1-mut* during endocrine-based therapy

ER+/HER2- BC can be treated with medicines called endocrine treatments or therapies (ET) that prevent the effect of oestrogen helping cancer cells grow. We call cancers that can be treated this way 'endocrine sensitive'. When the BC is advanced or metastatic, patients with endocrine-sensitive disease typically receive an ET with a medicine called a

CDK4/6i first; this is the standard of care (SOC) in the UK. A patient will usually only get chemotherapy if their organs are not working properly.

In the UK, there are several choices of endocrine-based treatment. The SOC is normally a type of medicine called an aromatase inhibitor (AI) such as anastrozole, exemestane or letrozole, taken with a CDK4/6i, such as palbociclib, ribociclib or abemaciclib (see Section 2c for further details). Both treatments work to reduce cancer growth; AIs reduce levels of the hormone oestrogen in the body and CDK4/6is interrupt the way that cancer cells divide and multiply. Even with this treatment, patients' cancer will eventually continue to grow. Some progress rapidly (circa 20%) and are usually considered to be unlikely to benefit from further ET.[12] Others progress more slowly, and for those patients, using a different type of ET may have benefits.[12]

When patients are taking ET, particularly an AI, and a CDK4/6i together, we have found that some patients 'acquire' genetic changes in their cancer. For this NICE review, the changes we are interested in are mutations in a gene called *ESR1 (ESR1-mut)*. *ESR1* is the gene that helps create an oestrogen receptor called ERα.[13] When this gene is mutated, it makes the ERα work in the absence of oestrogen and, as a consequence, makes the use of an AI obsolete (patients become resistant to treatment).[13, 14] *ESR1-mut*s in patients with ER+/HER2- advanced/mBC are more common the longer patients have been treated with ET.[12, 14–16] *ESR1-mut*s are found in up to 50% of patients with ER+/HER2- advanced/mBC whose disease progresses on an AI.[17, 18] Mutations in other genes can be found alongside *ESR1*, such as mutations in *PIK3CA*.

Number of patients with ER+/HER2- *ESR1*-mutated advanced/mBC

There are an estimated 600,000 people alive in the UK with a diagnosis of BC, with numbers also expected to rise to 1.2 million in 2030.[19] In the UK, rates are expected to increase to around 69,900 new cases of BC every year by 2038–2040.[20]

There is a lack of published data on the number of new and pre-existing cases of patients with ER+/HER2- *ESR1*-mutated advanced/mBC in England and Wales. This is because up until now, we have not had a treatment available that was recommended for use in patients with this mutation, so we were not measuring it. Based on published sources and clinical expert opinion, an estimated 2,559 patients are anticipated to be eligible to receive elacestrant in year 1 (see Budget Impact assessment for further details).

Current treatments for patients with ER+/HER2- *ESR1*-mutated advanced/mBC who have disease progression following ≥12 months of prior treatment with ET + CDK4/6i

Unless patients require immediate chemotherapy, for those with ER+/HER2- *ESR1*-mutated advanced/mBC who have disease progression following ≥12 months of prior treatment with ET + CDK4/6i, there are currently two treatment options used.

1) everolimus + exemestane (NICE TA421)[21]
2) alpelisib + fulvestrant (NICE TA816)[22] for patients with a single *PIK3CA-mut*, including those patients with both a *PIK3CA-mut* and an *ESR1-mut* (dual mutated population). Please see Section 2c for further details on comparators

Impact of BC: side effects of current treatments

Treatment side effects are a burden to patients, and they also contribute to reducing health-related quality of life (HRQoL). There are limitations to the current treatment options for patients with ER+/HER2- *ESR1*-mutated advanced/mBC who have disease progression following ≥12 months of prior treatment with ET + CDK4/6i. A high number of patients have side effects, and pain and inconvenience of treatment are associated with fulvestrant injections (that often require a trip to the hospital for its administration).[23–28]

Impact of BC: quality of life, financial, and social impact

ER+/HER2- advanced/mBC is an incurable, devastating disease. Five years after diagnosis, only about 36% of patients are still alive. As the cancer progresses, the likely success of treatment gets worse with each new line of therapy.[29–31] Patients with *ESR1-mut* have faster disease progression and worse survival than patients with ER+/HER2- advanced/mBC without an *ESR1-mut*.[32, 33]

Patients with ER+/HER2- advanced/mBC have poor quality of life (QoL), which gets worse as their disease progresses.[34, 35] Advanced/mBC causes substantial illness (physical symptoms e.g. pain, feeling sick and weight loss) and emotional problems (e.g. anxiety, depression, distress and isolation).[36–40] These issues negatively impact HRQoL and daily living, including physical activities, relationships, social life, work productivity and emotional well-being.[41, 42] See Section 2d for more discussion on living with BC.

The burden of caring for patients with cancer can also impact the patient's caregivers' physical and mental health and daily living (e.g. work status and social activities), negatively impacting HRQoL.[43, 44]

There is a high financial and societal burden associated with a diagnosis of BC. A recent report (published in January 2024) estimated the annual total cost of BC to the UK economy to be £2.6 to £2.8 billion.[45] Although the direct costs of BC to the NHS are large, societal costs make up the majority of this cost.[45] In 2024, the total well-being cost associated with BC (including patients' reduced HRQoL/early death, carer/partner well-being loss, and anxiety in children) is estimated at £17.5 billion.[45] This is not cash spent, but is representative of the human costs of BC.[45]

In summary, patients with ER+/HER2- *ESR1*-mutated advanced/mBC have faster disease progression and worse probable outcomes than patients without an *ESR1-mut*,[32, 33] and their HRQoL gets worse as their disease progresses.[35, 46]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

BC is diagnosed using a combination of clinical examination, imaging (ultrasound, computed tomography [CT], magnetic resonance imaging [MRI]), and looking at a sample of BC tissue under a microscope.[47–50]

To aid clinicians in making treatment decisions, testing of certain genes (genomic testing) has become a key part of treatment planning, and it is increasingly used at various points in the treatment pathway for patients with advanced/mBC.[51] Patients with ER+/HER2- advanced BC should only receive treatment with elacestrant if they have an *ESR1-mut*. To look for the *ESR1-mut*, a blood test is taken to look at circulating tumour DNA (ctDNA) in the plasma (the liquid part of blood where cells float); this is known as a liquid biopsy.[1]

As *ESR1-mut*s arise almost entirely after prior treatment with an AI in the advanced/metastatic setting and are typically not found in the tumour when it is first detected,[14] testing should be performed at disease progression – after one or more lines of ET.

In the UK, it is uncommon to take samples of BC tissue upon relapse following initial treatment.[3] In addition, mutations in the *ESR1* gene are more likely to be detected in liquid biopsy than on tissue biopsy. This highlights the importance of using liquid biopsies for *ESR1* testing, so clinicians can get results within a relevant timeframe to make informed treatment choices.

The NHS does not currently fund genomic testing for *ESR1-mut*s because elacestrant is the first available therapy for patients with ER+/HER2- *ESR1*-mutated advanced/mBC. Future funding is expected, in line with how genomic testing was introduced for treatments in BC with *PIK3CA-mut*.

2c) Current treatment options

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
    - Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

(See company submission, Document B, Section B.1.3.4)

Currently, there are no specific guidelines/guidance for the novel population of patients with ER+/HER2- *ESR1*-mutated advanced/mBC in England and Wales. The guidelines/guidance most consistent with clinical practice in England and Wales are NICE technology appraisals (TAs) for ER+/HER2- advanced/mBC, the European Society for Medical Oncology (ESMO) Guideline for mBC and the ESMO mBC Living Guideline for patients with ER+/HER2- mBC.[21, 22, 47, 52–60] Other NICE guidelines include NICE CG81 (advanced BC), last updated on 16 August 2017, and NICE Guideline (NG)101, (early and locally advanced BC), last updated on 16 January 2024.[49, 50]

NICE TA495, TA496 and TA563 recommend treatment with ET (i.e. an AI; anastrozole or letrozole) with a CDK4/6i (palbociclib, ribociclib or abemaciclib).[53–55] Treatment with chemotherapy is mainly reserved for patients with imminent organ failure.[3, 47, 52]

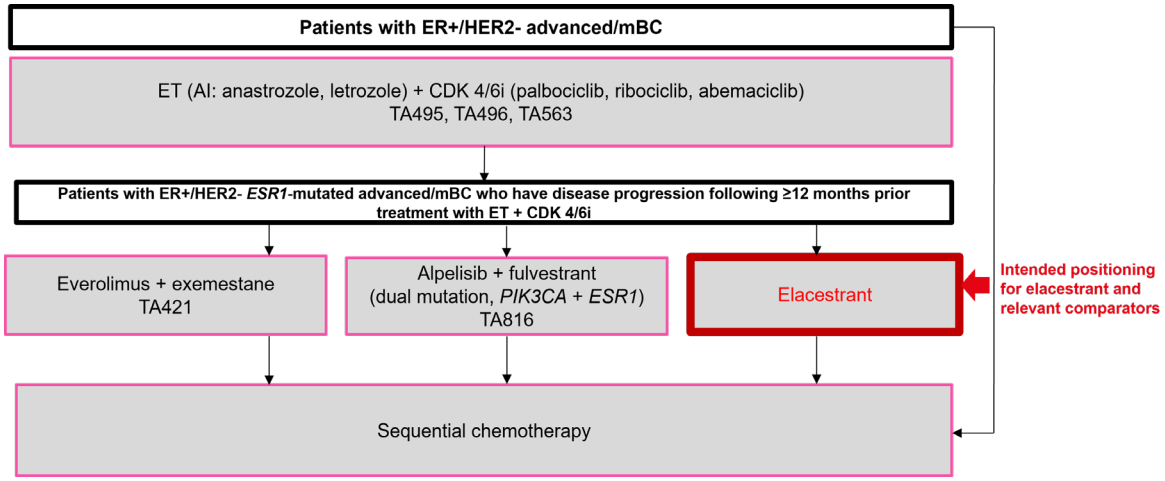
Unless patients require immediate chemotherapy, for those with ER+/HER2- *ESR1*-mutated advanced/mBC who have disease progression following ≥12 months prior treatment with ET + CDK4/6i, there are two treatment options that are used (see Section 2a):

1) everolimus + exemestane (NICE TA421)[21]
2) alpelisib + fulvestrant (NICE TA816):[22] used as a treatment option in patients with a single *PIK3CA-mut*, including those patients with both a *PIK3CA-mut* and an *ESR1-mut* (dual mutated)

BC specialist doctors in the UK have said that ETs either alone or in combination with chemotherapy are rarely used as a treatment in this population, and as such are not considered relevant comparators to elacestrant.[3]

BC specialist doctors in the UK anticipate that in clinical practice, elacestrant will be used in a smaller population than that of the marketing authorisation i.e. in postmenopausal women, and men, with ER+/HER2-, locally advanced/mBC with an activating *ESR1-mut* following ≥12 months of prior treatment with ET + CDK4/6i. The importance of time on prior ET in determining the best treatment for these patients is supported by the ESMO Living Guidelines (2023), which provide a strong recommendation for the use of elacestrant in patients with *ESR1*-mutated BC who had long progression-free survival (PFS) on prior ET + CDK4/6i.[52] Figure 1 shows the proposed place of elacestrant in the current treatment pathway in England and Wales.

Figure 1: Proposed positioning of elacestrant in the current treatment pathway



Abbreviations: AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER+, oestrogen receptor-positive; *ESR1*, oestrogen receptor 1 gene; ET, endocrine therapy; HER2-, human epidermal growth factor receptor 2-negative; mBC, metastatic breast cancer; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TA, technology appraisal

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Published evidence

Several publications have provided important information about patients' experiences of living with advanced/mBC. The instruments used to measure HRQoL in these publications are all suitable and validated for patients with BC.[61, 62]

Evidence shows that patients with ER+/HER2- advanced/mBC have poor QoL, which gets worse as their disease progresses.[34, 35] In a study of 96 patients with mBC in Germany, lower HRQoL scores across all HRQoL measures were reported in patients with mBC compared with those representing the average population.[63] In a survey of 235 patients with mBC in the UK who completed the Functional Assessment of Cancer Therapy - Breast (FACT-B), a self-administered questionnaire, scores for physical, social/family, emotional, and functional well-being were lower (reflecting worse HRQoL) for patients with mBC compared with those for patients with less severe disease.[42, 64]

Disease progression decreases HRQoL with each extra line of therapy. In a study examining HRQoL in 100 patients with mBC in the UK, disease progression had the largest impact on HRQoL.[46] A further study, conducted in 613 people in five European countries and 126 people in the US, found that in patients with ER+/HER2- advanced/mBC, patients on second-line therapy reported significantly lower mean EuroQol-5 Dimension (EQ-5D) index scores compared with those for patients on first-line therapy.[35]

Advanced/mBC causes substantial illness (physical symptoms e.g. pain, feeling sick and weight loss) and emotional problems (e.g. anxiety, depression, distress and isolation).[36–40]

These issues negatively impact HRQoL and daily living, including physical activities, relationships, social life, work productivity and emotional well-being.[41, 42]

More than half of women with mBC (58%), report their family well-being is 'very much' impacted, and a fifth (20%) report the disease has greatly affected their responsibilities and social life.[65] Approximately 36% of women state that they no longer work and were forced to retire due to their disease.[65, 66] The impact of BC on work is further highlighted by a US study, which reported BC progression was linked with a low probability of employment and increased hours missed in the workplace.[67]

In a US study of 15 patients with HR+/HER2- advanced/mBC, patients reported that their disease impacted leisure activities (67%), the ability to maintain relationships (47%), work status (27% moved from full-time to part-time work), and sleeping due to pain and discomfort (27%).[41] The most frequently reported physical functioning impacts were on housework (73%), walking (73%) and cooking (73%).[41]

Examples of published quotes from patients with HR+/HER2- advanced/mBC illustrate the negative impact the disease has on their lives:

- "*I don't want to do [anything]. Eat, cook, clean, nothing. I'm just that tired and I'll go right to sleep".*[41]
- "*You don't want to walk long distances unless you're with someone. Even if you're with someone you don't want to walk long distances because you become tired quicker".*[41]
- *"I know that I'm a very good cook but now, in the kitchen, that's tiresome".*[41]

The additional burden from treatment (see Section 2a) is also important. In a study of 467 patients with HR+/HER2- advanced/mBC across seven countries, 82% of patients experienced at least one moderate- or severe-grade side effect since starting treatment, and 67% and 20% of patients experienced at least three and five side effects, respectively.[68] The majority of these patients (78%) believed that treatment side effects were affecting their daily lives and had a moderate or severe impact on their HRQoL.[68]

In summary, there is a lot of evidence published indicating that advanced/mBC is detrimental to the QoL of patients.

Patient-focused evidence with elacestrant

Patient-reported outcomes (PROs) for elacestrant have been described in the EMERALD trial for patients with ER+/HER2-, locally advanced or mBC with an activating *ESR1-mut* who had disease progression following at least one line of ET including a CDK4/6i. These outcomes were obtained from questionnaires designed to capture the impact of treatment on patients' QoL.

In EMERALD, patient outcomes were reported using three different PRO tools: the EuroQol 5 Dimension 5 Level (EQ-5D-5L), the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30) and the Patient-Reported Outcome Common Terminology Criteria for Adverse Events (PRO-CTCAE) questionnaires. These were completed periodically throughout the treatment period, at the end of treatment (± 14 days), and then at the post-treatment safety follow-up visit 30 days after the last dose of the study drug (± 3 days).[69] Overall, QoL was maintained between treatment groups in the EMERALD trial and over time. This means the scores didn't get better or worse (see Section 3f for full details).

Additionally, safety data were collected to ensure the safety profile of elacestrant is well-understood and manageable for this patient population. During the treatment period for EMERALD, elacestrant showed a predictable and manageable safety profile that is consistent with other ETs (see Section 3g for more details).[69, 70]

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

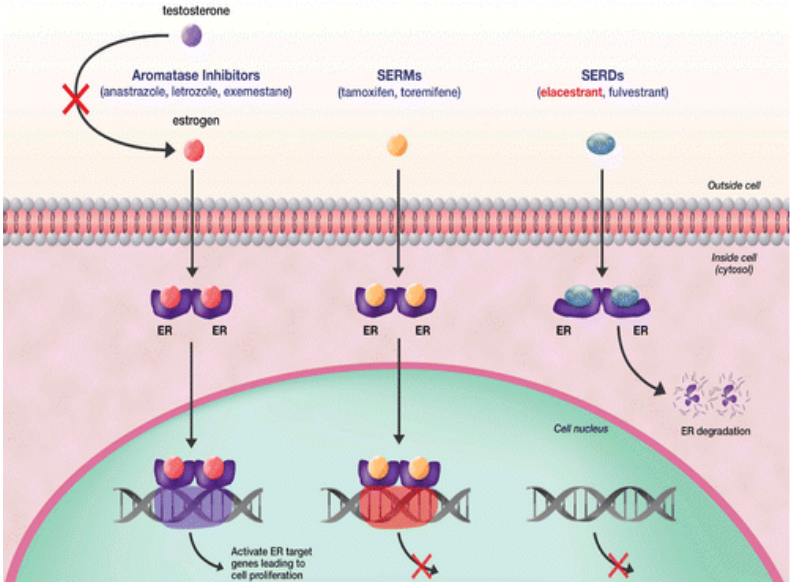
If there are relevant documents which have been produced to support your regulatory submission such as a Summary of Product Characteristics or patient information leaflet, please provide a link to these.

How does elacestrant work?

Elacestrant is an ET taken by mouth that belongs to a family called 'selective oestrogen receptor degraders (SERDs)'. It binds to the ER, enables its break down and slows oestrogen-dependent cancer growth, including in people with changes (mutations) to *ESR1* and those resistant to CDK4/6i and fulvestrant (Figure 2).[70–72]

Changes in *ESR1* lead to activation of the ER independently of the presence of oestrogen. As a consequence, the cancer can continue to grow and there is loss of sensitivity to further treatment with AIs. However, other ETs such as ER degraders (SERDs), have a different mechanism of action from AIs, and remain efficacious.[70, 73] Therefore, whilst patients with ER+/HER2- *ESR1*-mutated advanced/mBC who have disease progression following ≥12 months of prior therapy with ET + CDK4/6i are unlikely to benefit from further AI treatment, they do have the potential to benefit from treatment with elacestrant.

Figure 2: Elacestrant mechanism of action



Abbreviations: ER, oestrogen receptor; SERD, selective oestrogen receptor degrader; SERM, selective oestrogen receptor modulator
Source: Bardia *et al.* (2019)[71]

Why is elacestrant innovative?

There are currently no other licensed oral treatment options specifically for advanced/mBC patients with an *ESR1-mut*. Elacestrant is the first oral SERD licensed for this novel population of patients. [23–28]

Please refer to the Summary of Product Characteristics (SmPC)[1] and Patient Information Leaflet[74] for more details about the way this treatment works.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Elacestrant is to be taken on its own and not in combination with any other drug.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Elacestrant is to be taken by mouth as a tablet (345 mg) once daily, as long as the patient is benefiting from treatment or until unacceptable side effects occur. Tablets should be swallowed whole, and patients should take their dose at approximately the same time each day with a light meal to reduce the risk of feeling sick and vomiting.[1] Doses can be reduced or modified depending on side effects as per the SmPC.[1]

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Evidence for elacestrant for the treatment of patients with ER+/HER2- *ESR1*-mutated advanced/mBC who have disease progression following ≥12 months of prior treatment with ET + CDK4/6i comes from a subgroup of patients in the EMERALD trial. EMERALD was a randomised trial, run across 228 sites in 17 countries.[69, 70] Of the 478 patients who were enrolled (All Patients), 228 had an *ESR1-mut* (marketing authorisation population) and 159 had an *ESR1-mut* and had received ≥12 months of prior ET + CDK4/6i (population relevant to this appraisal).[69, 75] See *company submission, Document B, Section B.2.3.1 (Table 7)* for detailed inclusion and exclusion criteria. In total, 115 patients with *ESR1-mut* were randomly assigned to elacestrant and 113 patients to SOC.[69, 70] In the relevant subgroup of patients (patients with *ESR1-mut* who had received ≥12 months of prior ET + CDK4/6i), 78 were in the elacestrant group and 81 in the SOC group.[2, 4, 75]

Choice of SOC treatment was decided by the responsible physician, and could be one of fulvestrant, anastrozole, letrozole, or exemestane alone. The study was open-label, meaning each patient and their physicians knew which treatment they were being given. However, patients, physicians, and the study personnel were not aware of the aggregated results from the trial until after predetermined ‘database locks’ (dates on which

subsequently collected data were not considered as part of the analysis) and/or their analysis and publications. Where possible, study personnel were also blinded to treatment assignment until after database lock (i.e. the personnel performing statistical analyses and those responsible for reviewing images and clinical information collected on-study to determine the endpoints of disease response and progression).[69]

The key reported outcome was PFS (assessed by imaging review committee), defined as the length of time from randomisation until the date of objective disease progression or death from any cause. The key secondary endpoint was overall survival (OS), defined as the length of time from randomisation until the date of death from any cause. Additional secondary endpoints included response rate, PROs (these outcomes subjectively measured patients' HRQoL and relied on information from questionnaires that patients themselves had answered) and safety outcomes, including overall and treatment-related adverse reactions.[69]

The first data cut (6 September 2021) was for the analysis of the primary efficacy endpoint (PFS) and additional secondary endpoints. An interim survival analysis occurred at that timepoint for the key secondary endpoint OS, and the final survival analysis occurred after the second data cut (2 September 2022).[69, 76]

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Progression-free survival

(See company submission, Document B, Section B.2.6.1, B.2.7.2.1 and B.2.7.3.1)

In EMERALD, treatment with elacestrant significantly reduced the risk of progression or death vs. SOC by 45% in all patients with *ESR1-mut*.[70]

In the *post hoc* subgroup analysis of patients with *ESR1-mut* with ≥12 months of prior ET + CDK4/6i, patients treated with elacestrant had a greater improvement in PFS (8.6 months) vs. SOC (1.9 months); an absolute increase of 6.7 months in median PFS.[2, 4, 75] The analysis in those patients who were dual mutated (i.e. *ESR1-mut, PIK3CA-mut* and who had received ≥12 months of prior ET + CDK4/6i) showed an absolute increase of 3.51 months in median PFS observed with elacestrant (5.45 months) vs. SOC (1.94 months).[2, 77]

In patients with *ESR1-mut*, the benefit in PFS for elacestrant vs. SOC was sustained across multiple analysis points, demonstrating a robust and durable improvement in PFS vs. SOC.[69, 70] In the *post hoc* subgroup analysis of patients with *ESR1-mut* with ≥12 months of prior ET + CDK4/6i, 35.81% of patients treated with elacestrant were free of disease progression at 12 months vs. 8.39% in the SOC group, a 4-fold increase in the rates of patients remaining alive and free of progression at 1 year. [4, 75]

Overall survival

See company submission, Document B, Section B.2.6.2, B.2.7.2.2 and B.2.7.3.2

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient-reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

(See company submission, Document B, Section B.2.6.4, B.2.7.2.3 and B.2.7.3.3)

Patient QoL was measured in EMERALD using the following patient-reported questionnaires: the EQ-5D-5L, the EORTC-QLQ-C30 and the PRO-CTCAE. These are questionnaires that have been designed and approved to help capture the QoL of patients whilst they take part in a trial. These were completed periodically throughout the treatment period, at the end of treatment (± 14 days), and then at the post-treatment safety follow-up visit 30 days after the last dose of the study drug (± 3 days).[69]

QoL was maintained between treatment groups in the EMERALD trial and over time. This means the scores didn't get better or worse. EORTC-QLQ-C30 scores were generally similar across treatment groups and time. PRO-CTCAE results showed no clinically meaningful differences between treatment groups, and no noteworthy changes over time (from the start of treatment) in either group for change in patient-reported frequency, severity, and interference of symptoms from any side effect. EQ-5D-5L scores were comparable across treatment groups with no notable differences over time and no meaningful change from baseline.[78, 79] Results were similar in the two *post hoc* subgroup analyses.

In summary, patients taking elacestrant maintained a stable disease state for longer, lessening disruption to usual activities and work, with no detrimental effect on their QoL.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

(See company submission, Document B, Section B.2.10, B.2.7.2.4 and B.2.7.3.4)

During the treatment period for EMERALD, elacestrant showed a predictable and manageable safety profile that is consistent with other ETs.[69, 70] The side effects reported for patients with *ESR1-mut* and All Patients were generally similar.[69, 70]

Among patients with *ESR1-mut* and All Patients, side effects in both treatment groups were mainly mild to moderate (Grade 1 and 2). The incidence of severe/life-threatening (Grade 3 or 4) side effects was low in both treatment groups, with no single side effect exceeding 5%.

Among patients with *ESR1-mut*, there was a similar rate of side effects reported for elacestrant and SOC (91.3% for elacestrant and 86.8% for SOC). The four most common side effects reported for elacestrant and SOC among patients with *ESR1-mut* included feeling sick (34.8% vs. 17.9%), pain in the joints (20% vs. 17.9%), vomiting (18.3% vs. 9.4%) and tiredness (17.4% vs. 19.8%). SOC had higher rates of abnormal liver function blood tests (increased aspartate aminotransferase [14.2% vs. 10.4%] and increased alanine aminotransferase [12.3% vs. 5.2%]) and injection site pain (only reported for those on SOC). The most common treatment-related side effects among patients with *ESR1-mut* reported for both elacestrant and SOC were feeling sick (22.6% vs. 12.3%) and tiredness (12.2% vs. 11.3%).[69]

Among patients with *ESR1-mut* there were very low rates of side effects leading to a dose reduction (6 [5.2%] vs. 0) or stopping treatment (6 [5.2%] vs. 4 [3.8%]) for elacestrant and SOC, respectively. A higher incidence of dose interruption (which means the treatment was stopped temporarily) was recorded for patients taking elacestrant vs. SOC (25 [21.7%] vs. 7 [6.6%]). There were four on-study deaths in the patients with *ESR1-mut*, but none of these was thought to be treatment-related. A similar, and low, proportion of serious side effects was reported across the two treatment groups (14 [12.2%] for elacestrant vs. 12 [11.3%] for SOC), with no single side effect having a frequency ≥2%. Among patients with *ESR1-mut*, no serious side effects were thought to be treatment-related in the SOC group and only 2 (1.7%) were deemed to be treatment-related in the elacestrant group. Safety data for the two *post hoc* subgroups were consistent with those reported for All Patients and patients with *ESR1-mut*.[69]

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration.

Improvement in progression-free survival

In EMERALD, patients with *ESR1-mut* taking elacestrant demonstrated a statistically significant and clinically meaningful 45% reduction in the risk of progression or death vs. SOC treatment.[70] The improvement in PFS for elacestrant vs. SOC was sustained across multiple analysis points, demonstrating a robust and durable improvement in PFS vs. SOC.[70] Benefit was also seen in the *post hoc* subgroup analysis of patients with *ESR1-mut* with ≥12 months of prior ET + CDK4/6i, where patients treated with elacestrant had a greater improvement in PFS (8.6 months) vs. SOC (1.9 months), an absolute increase of 6.7 months in median PFS.[2, 4, 75] Benefit was also seen in the dual mutated population (*ESR1-mut, PIK3CA-mut* and ≥12 months of prior ET + CDK4/6i), with an absolute increase of 3.51 months in median PFS observed with elacestrant (5.45 months) vs. SOC (1.94 months).[2, 77]

Manageable safety profile

Amongst patients with *ESR1-mut*, side effects in both treatment groups were mainly mild to moderate (Grade 1 and 2). The rate of serious/life-threatening (Grade 3 or 4) side effects was low in both treatment groups, with no single side effect exceeding 5%. Elacestrant has a well-tolerated and manageable safety profile, with a low stopping rate (5.2% elacestrant vs. 3.8% SOC). Compared with SOC, patients had lower rates of abnormal liver function blood tests (increased aspartate aminotransferase [10.4% vs. 14.2%] and alanine aminotransferase [5.2% vs. 12.3%]) and were able to avoid effects associated with the injection of fulvestrant, such as pain, swelling and itch.[69]

Maintains quality of life and is convenient for patients

QoL was maintained between treatment groups in the EMERALD trial and over time. By allowing patients to maintain a stable disease state for longer, elacestrant lessens disruption to usual activities and work. In addition, elacestrant offers a convenient mode of administration that meets patient preferences with an at-home, once-daily treatment that can be taken by mouth. Patients with advanced/mBC prefer treatments taken by mouth, that allow them to continue their normal lives without the pain and inconvenience of injections.[80] Oral treatments for patients with *ESR1*-mutated tumours may reduce healthcare use and provide convenience for both patients and carers (by avoiding frequent visits to clinics for treatment administration), especially important when patients are experiencing tiredness.

The first oral treatment option to demonstrate activity in tumours with an *ESR1-mut*

There are currently no treatment options specifically indicated for *ESR1*-mutated BC. Although the combinations of everolimus + exemestane and alpelisib + fulvestrant may be options for patients with ER+/HER2- *ESR1*-mutated advanced/mBC who have disease progression following ≥12 months of prior treatment with ET + CDK4/6i, there is uncertainty regarding their efficacy due to lack of data in this patient population. Understanding how to overcome the acquired resistance to further ET due to *ESR1-mut*s is an important consideration when treating patients with ER+/HER2- *ESR1*-mutated advanced/mBC.[71, 81]

In summary, elacestrant is the first oral SERD treatment to demonstrate superiority in PFS over SOC ET in patients with ER+/HER2- *ESR1*-mutated, locally advanced or mBC post-CDK4/6i.[70]

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

As with most cancer treatments, treatment with elacestrant is associated with side effects (Section 3g).

Amongst patients with *ESR1-mut*, elacestrant had higher rates of feeling sick (34.8% vs. 17.9%), pain in the joints (20% vs.17.9%) and vomiting (18.3% vs. 9.4%) vs. SOC. In contrast, SOC had higher rates of tiredness (19.8% vs. 17.4%), abnormal liver function blood tests (increased aspartate aminotransferase [14.2% vs. 10.4%] and alanine aminotransferase [12.3% vs. 5.2%]) and injection site pain (only reported for those on SOC). Overall, there was a similar rate of side effects reported for elacestrant and SOC (91.3% for elacestrant and 86.8% for SOC).

A higher proportion of side effects were regarded to be treatment-related in the elacestrant group (61.7%) than in the SOC group (46.2%), with the most common being feeling sick (22.6% vs. 12.3%) and tiredness (12.2% vs. 11.3%) for elacestrant vs. SOC. Side effects in both treatment groups were mainly mild to moderate (Grade 1 and 2). The incidence of severe/life-threatening (Grade 3 or 4) side effects was low in both treatment groups, with no single side effect exceeding 5%.[69]

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?

- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Cost-effectiveness model

There are no existing economic models which assess the cost-effectiveness of elacestrant for treating patients with ER+/HER2- *ESR1*-mutated advanced/mBC who have disease progression following ≥12 months of prior treatment with ET + CDK4/6i. Therefore, a new cost-effectiveness model was developed for this submission.

The economic model was designed to assess elacestrant in two groups of patients:

1. *ESR1-mut* and prior ET + CDK4/6i ≥12 months
2. Dual mutated (both *ESR1-mut* and *PIK3CA-mut*) and prior ET + CDK4/6i ≥12 months

Data from the EMERALD clinical trial was used to inform the effectiveness of elacestrant in the economic model. The control arm in EMERALD was SOC, comprising fulvestrant, exemestane, letrozole or anastrozole. As the treatments administered in the EMERALD SOC arm are not representative of UK practice, real-world data were obtained to inform the effectiveness of the relevant comparators for each population.

Cost-effectiveness analysis for Population #1

For patients with ER+/HER2- *ESR1*-mutated advanced/mBC who have disease progression following ≥12 months prior treatment with ET + CDK4/6i, current treatment is with everolimus in combination with exemestane (everolimus + exemestane). Therefore, a cost-effectiveness model was designed to compare elacestrant to everolimus + exemestane in this population. Data from the EMERALD clinical trial was used to inform the effectiveness of elacestrant. Real-world data were obtained (from the Flatiron database) to inform the effectiveness of everolimus + exemestane. Statistical adjustments were made to the data to account for differences in patient characteristics between the clinical trial and real-world populations. This approach aims to reduce bias in the effectiveness estimates for elacestrant and everolimus + exemestane.

Compared to everolimus + exemestane, the analysis estimates that elacestrant increases the amount of time spent in the progression-free health state, and therefore extends life by delaying disease progression.

The model also shows that elacestrant improves QoL because of prolonged time in the progression-free state where symptoms are anticipated to be less severe compared to the progressed disease health state.

The cost of treatment is greater for elacestrant vs. everolimus + exemestane.

Base case results demonstrate that elacestrant is associated with a deterministic incremental cost effectiveness ratio (ICER) of £24,873. This takes into account the 1.2x severity modifier. It should be noted that the decision making ICERs considered by committee may be different to these ICERs, due to comparator discounts.

Cost-effectiveness analysis for Population #2

For patients with ER+/HER2- advanced/mBC who have disease progression following ≥12 months of prior treatment with ET + CDK4/6i and have a tumour that is dual mutated (*ESR1-mut* and *PIK3CA-mut*), current treatment is with alpelisib in combination with fulvestrant (alpelisib + fulvestrant). Therefore, a cost-effectiveness model was designed to compare elacestrant to alpelisib + fulvestrant. Data from the EMERALD clinical trial was used to inform the effectiveness of elacestrant. Real-world data were obtained (from the Flatiron database) to inform the effectiveness of alpelisib + fulvestrant. Statistical adjustments were made to the data to account for differences in patient characteristics between the clinical trial and real-world populations. This approach aims to reduce bias in the effectiveness estimates for elacestrant and alpelisib + fulvestrant.

The analysis estimates patients treated with elacestrant spend slightly longer in the progression-free health state vs. alpelisib + fulvestrant.

The cost of treatment is lower for elacestrant vs. alpelisib + fulvestrant. There are also important cost reductions for elacestrant vs. alpelisib + fulvestrant, as visits to see a healthcare practitioner are required for administration of fulvestrant injections but elacestrant is self-administered at home.

Base case results demonstrate that elacestrant is associated with a net monetary benefit (NMB) of £20,451 versus alpelisib + fulvestrant. No severity modifier is applied for this comparison. It should be noted that the decision making ICERs considered by committee may be different to these ICERs, due to comparator discounts.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

In patients with ER+/HER2- *ESR1*-mutated advanced/mBC who have disease progression after ≥12 months of prior treatment with ET + CDK4/6i, the key issues associated with current treatment are:

1. the unmet need for a treatment with proven efficacy in the presence of an acquired *ESR1-mut*
2. treatment-related side effects with current treatment options, which limit their use (see Section 2a).

Elacestrant helps address these issues by:

1. Demonstrating efficacy in patients with advanced/mBC who have acquired an *ESR1-mut*
2. Being an oral medicine that is well-tolerated (providing ease for patients and caregivers).

Specifically, elacestrant significantly reduced the risk of progression or death vs. SOC by 45% in patients with *ESR1-mut*,[70] with greater improvement seen for patients with longer exposure to prior ET + CDK4/6i (the *post hoc* subgroup who had ≥12 months of prior ET + CDK4/6i), with an absolute increase of 6.7 months in median PFS.[2, 4, 75] Importantly, the benefit in PFS for elacestrant vs. SOC was sustained across multiple analysis points, demonstrating a robust and durable improvement in PFS vs. SOC.[69, 70] There was a 4-fold increase in the rates of patients remaining alive and free of progression at 1 year in the *post hoc* subgroup analysis of patients with *ESR1-mut* with ≥12 months of prior ET + CDK4/6i, with 35.81% free of progression at 12 months in the elacestrant group vs. 8.39% in the SOC group.[4, 75]

Benefits not captured in the cost-effectiveness analysis

Societal costs of advanced/mBC are not included in the economic evaluation in this submission. However, it is important to consider the positive benefits that new treatment options could provide i.e. improved PFS is likely to lead to increased work productivity and reduced absenteeism for both patients and carers.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
No equality issues were identified for this patient population.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open-access materials or provide copies that patients can access.

Information related to BC:

- Cancer Research UK
- Macmillan Cancer Support
- Breast Cancer UK
- Breast Cancer Now
- NHS
- Make 2nds Count
- MET UP UK

Key published EMERALD clinical trial data:

- Bidard *et al. J Clin Oncol.* 2022;40(28):3246-3256l. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer: Results From the Randomized phase III EMERALD Trial[70]
- Cortés *et al,* 2023. EMERALD trial analysis of patient-reported outcomes (PROs) in patients with ER+/HER2− advanced or metastatic breast cancer (mBC) comparing oral elacestrant vs. standard of care (SOC) endocrine therapy. Presented at the 2023 ESMO Breast Cancer Symposium. May 11, 2023. Abstract 185O.[79]
- Bardia *et al,* 2022. EMERALD phase III trial of elacestrant versus standard of care endocrine therapy in patients with ER+/HER2- metastatic breast cancer: Updated results by duration of prior CDK4/6i in metastatic setting. Presented at the 2022 San Antonio Breast Cancer Symposium (SABCS). December 8, 2022. Abstract GS3-01by Kaklamani V.[4]
- Bardia *et al,* 2023. Elacestrant vs. standard-of-care in ER+/HER2- advanced or metastatic breast cancer (mBC) with *ESR1* mutation: key biomarkers and clinical subgroup analyses from the phase III EMERALD trial. Poster presented Friday, December 8, 2023 by Lu J[2]

Further information:

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/

- European Observatory on Health Systems and Policies. Health technology assessment – an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

Other:

- Curigliano *et al*. *Ann Oncol.* 2021;32(12):1475-1495. ESMO Metastatic Breast Cancer Living Guidelines, v1.1 May 2023. https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline[52]

4b) Glossary of terms

ctDNA – Circulating tumour DNA is tumour-derived fragmented DNA in the bloodstream that is not associated with cells.

ER – Oestrogen receptors are proteins found inside cells that are activated by the hormone oestrogen.

ESR1 – oestrogen receptor 1 is a protein-coding gene that encodes an oestrogen receptor and ligand-activated transcription factor. *ESR1* has been a focus in breast cancer for quite some time, but is also clinically relevant in endometrial, ovarian and other cancer types.

HER2 – a protein (receptor) found on the surface of cells. In excess, it can encourage cancer cells to divide and grow.

HR – A hormone receptor is a molecule that binds to a specific hormone.

ICER – an incremental cost-effectiveness ratio is a summary measure representing the economic value of an intervention, compared with an alternative (comparator). It is usually the main output or result of an economic evaluation. An ICER is calculated by dividing the difference in total costs (incremental cost) by the difference in the chosen measure of health outcome or effect (incremental effect) to provide a ratio of 'extra cost per extra unit of health effect' – for the more expensive therapy vs the alternative.

Marketing authorisation – Permission to sell a medicine after the evidence (on safety, quality, and efficacy) has been assessed. This is different from NICE's appraisal of a medicine, which also considers whether the medicine is cost-effective for the NHS.

Mutation – An alteration in the genetic material (the genome) of a cell of a living organism or of a virus that is more or less permanent and that can be transmitted to the cell's or the virus's descendants.

Open-label trial – A trial where patients and physicians have knowledge of the assigned treatment.

Phase III – A clinical study that investigates how safe and efficacious a medicine is. The medicine will previously have been tested in phase I–II studies, which test whether the medicine is safe enough to use in humans and has an effect on the disease.

PIK3CA – phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha is a protein-coding gene. It is the most recurrently mutated gene in breast cancer.

Randomised trial – A study in which a number of similar people are randomly assigned to two (or more) groups to test a specific drug or other intervention against a control (i.e. a group being given the medicine or a group being given a comparator).

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. MHRA. Summary of Product Characteristics (KORSERDU). Medicines and Healthcare products Regulatory Agency; 2023.

2. Bardia A. PS17-02 Elacestrant vs standard-of-care in ER+/HER2- advanced or metastatic breast cancer (mBC) with *ESR1* mutation: key biomarkers and clinical subgroup analyses from the phase 3 EMERALD trial. *SABCS*. 2023.
3. Menarini Stemline. UK Clinical Expert Opinion, Data on File. 2024.
4. Bardia A, Bidard F-C, Neven P, *et al.* Abstract GS3-01: GS3-01 EMERALD phase 3 trial of elacestrant versus standard of care endocrine therapy in patients with ER+/HER2- metastatic breast cancer: Updated results by duration of prior CDK4/6i in metastatic setting. *Cancer Research*. 2023;83(5_Supplement):GS3-01. https://doi.org/10.1158/1538-7445.SABCS22-GS3-01.
5. Globocan. Cancer populations factsheet: United Kingdom. World Health Organization: International Agency for Research on Cancer; 2022.
6. Cancer Research UK. What is breast cancer? Last accessed: 08/10/2023. https://www.cancerresearchuk.org/about-cancer/breast-cancer/about.
7. Cardoso F, Paluch-Shimon S, Senkus E, *et al.* 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Annals of Oncology*. 2020;31(12):1623–1649. https://doi.org/10.1016/j.annonc.2020.09.010.
8. Cardoso F, Costa A, Norton L, *et al.* ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). *Breast*. 2014;23(5):489–502. https://doi.org/10.1016/j.breast.2014.08.009.
9. Cancer Research UK. Proportion of Cancer Cases by Stage at Diagnosis. Last accessed: 08/11/2023. https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/.
10. Dewis R, Gribbin J. Breast Cancer: Diagnosis and Treatment: An Assessment of Need. *Breast Cancer: Diagnosis and Treatment: An Assessment of Need*. National Collaborating Centre for Cancer (UK); 2009.
11. SEER. Cancer Stat Facts: Female Breast Cancer Subtypes. Last accessed: 08/10/2023. https://seer.cancer.gov/statfacts/html/breast-subtypes.html.
12. Cogliati V, Capici S, Pepe FF, *et al.* How to Treat HR+/HER2- Metastatic Breast Cancer Patients after CDK4/6 Inhibitors: An Unfinished Story. *Life (Basel)*. 2022;12(3):378. https://doi.org/10.3390/life12030378.
13. Chen Y-C, Yu J, Metcalfe C, *et al.* Latest generation estrogen receptor degraders for the treatment of hormone receptor-positive breast cancer. *Expert Opin Investig Drugs*. 2022;31(6):515–529. https://doi.org/10.1080/13543784.2021.1983542.
14. Brett JO, Spring LM, Bardia A, Wander SA. *ESR1* mutation as an emerging clinical biomarker in metastatic hormone receptor-positive breast cancer. *Breast Cancer Res*. 2021;23(1):85. https://doi.org/10.1186/s13058-021-01462-3.
15. Jeselsohn R, Yelensky R, Buchwalter G, *et al.* Emergence of constitutively active estrogen receptor-α mutations in pretreated advanced estrogen receptor positive breast cancer. *Clin Cancer Res*. 2014;20(7):1757–1767. https://doi.org/10.1158/1078-0432.CCR-13-2332.
16. Chaudhary N, Chibly AM, Collier A, *et al.* CDK4/6i-treated HR+/HER2- breast cancer tumors show higher *ESR1* mutation prevalence and more altered genomic landscape. *npj Breast Cancer*. 2024;10(1):1–12. https://doi.org/10.1038/s41523-024-00617-7.
17. Jhaveri KL, Jeselsohn R, Ma CX, *et al.* Imlunestrant, with or without everolimus or alpelisib, in ER+, HER2- advanced breast cancer (aBC): Results from the phase 1a/b EMBER study. n.d.
18. Lin NU, Borges VF, Patel MR, *et al.* Results from the phase 1/2 study of OP-1250, an oral complete estrogen receptor (ER) antagonist (CERAN) and selective ER degrader (SERD) in patients (pts) with advanced or metastatic ER-positive, HER2-negative breast cancer. *Annals of Oncology*. n.d.;34(S2):S338. https://doi.org/10.1016/j.annonc.2023.09.559.
19. Breast Cancer Now. Breast cancer facts and statistics. 2024. Last accessed: 02/21/2024. https://breastcancernow.org/about-us/why-we-do-it/breast-cancer-facts-and-statistics/#diagnosis-statistics.
20. Cancer Research UK. Breast cancer incidence (invasive statistics). Last accessed: 04/12/2024. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive#heading-Zero.
21. NICE. Everolimus with exemestane for treating advanced breast cancer after endocrine therapy: TA421. National Institute for Health and Care Excellence; 2016.
22. NICE. Alpelisib with fulvestrant for treating hormone receptor-positive, HER2-negative, *PIK3CA*-mutated advanced breast cancer: TA816. National Institute for Health and Care Excellence; 2022.
23. Novartis. Everolimus (AFINITOR): full prescribing information. 2022.
24. Novartis. Alpelisib (PIQRAY): full prescribing information. 2022.

25. AstraZeneca. Fulvestrant (FASLODEX): full prescribing information. 2011.
26. Baselga J, Campone M, Piccart M, *et al.* Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med*. 2012;366(6):520–529. https://doi.org/10.1056/NEJMoa1109653.
27. Rugo HS, Pritchard KI, Gnant M, *et al.* Incidence and time course of everolimus-related adverse events in postmenopausal women with hormone receptor-positive advanced breast cancer: insights from BOLERO-2. *Ann Oncol*. 2014;25(4):808–815. https://doi.org/10.1093/annonc/mdu009.
28. André F, Ciruelos E, Rubovszky G, *et al.* Alpelisib for *PIK3CA*-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. *N Engl J Med*. 2019;380(20):1929–1940. https://doi.org/10.1056/NEJMoa1813904.
29. Valachis A, Carlqvist P, Ma Y, *et al.* Overall survival of patients with metastatic breast cancer in Sweden: a nationwide study. *Br J Cancer*. 2022;127(4):720–725. https://doi.org/10.1038/s41416-022-01845-z.
30. Grinda T, Antoine A, Jacot W, *et al.* Evolution of overall survival and receipt of new therapies by subtype among 20 446 metastatic breast cancer patients in the 2008-2017 ESME cohort. *ESMO Open*. 2021;6(3):100114. https://doi.org/10.1016/j.esmoop.2021.100114.
31. Kurosky SK, Mitra D, Zanotti G, Kaye JA. Treatment Patterns and Outcomes of Patients With Metastatic ER+/HER-2- Breast Cancer: A Multicountry Retrospective Medical Record Review. *Clin Breast Cancer*. 2018;18(4):e529–e538. https://doi.org/10.1016/j.clbc.2017.10.008.
32. Kalinsky K, Accordino MK, Chiuzan C, *et al.* Randomized Phase II Trial of Endocrine Therapy With or Without Ribociclib After Progression on Cyclin-Dependent Kinase 4/6 Inhibition in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer: MAINTAIN Trial. *J Clin Oncol*. 2023;41(24):4004–4013. https://doi.org/10.1200/JCO.22.02392.
33. Turner NC, Swift C, Kilburn L, *et al. ESR1* Mutations and Overall Survival on Fulvestrant versus Exemestane in Advanced Hormone Receptor-Positive Breast Cancer: A Combined Analysis of the Phase III SoFEA and EFECT Trials. *Clin Cancer Res*. 2020;26(19):5172–5177. https://doi.org/10.1158/1078-0432.CCR-20-0224.
34. Davie A, Carter GC, Rider A, *et al.* Real-world patient-reported outcomes of women receiving initial endocrine-based therapy for HR+/HER2− advanced breast cancer in five European countries. *BMC Cancer*. 2020;20(1):855. https://doi.org/10.1186/s12885-020-07294-2.
35. Mitra D, Wood R, Courcy JD, Iyer S. Patient Reported Health Utility in HR+/HER2-Advanced/Metastatic Breast Cancer. *Value in Health*. 2016;19(7):A749. https://doi.org/10.1016/j.jval.2016.09.2297.
36. Breast Cancer Now. Global Status of Advanced/Metastatic Breast Cancer 2005-2015 Decade Report. Last accessed: 02/16/2024. https://breastcancernow.org/sites/default/files/global_status_of_metastatic_breast_cancer_2005_to_2015_decade_report_summary.pdf.
37. Koo MM, von Wagner C, Abel GA, McPhail S, Rubin GP, Lyratzopoulos G. Typical and atypical presenting symptoms of breast cancer and their associations with diagnostic intervals: Evidence from a national audit of cancer diagnosis. *Cancer Epidemiol*. 2017;48:140–146. https://doi.org/10.1016/j.canep.2017.04.010.
38. Cancer Research UK. Symptoms of breast cancer. Last accessed: 04/12/2024. https://www.cancerresearchuk.org/about-cancer/breast-cancer/symptoms.
39. İzci F, İlgün AS, Fındıklı E, Özmen V. Psychiatric Symptoms and Psychosocial Problems in Patients with Breast Cancer. *J Breast Health*. 2016;12(3):94–101. https://doi.org/10.5152/tjbh.2016.3041.
40. Reich M, Lesur A, Perdrizet-Chevallier C. Depression, quality of life and breast cancer: a review of the literature. *Breast Cancer Res Treat*. 2008;110(1):9–17. https://doi.org/10.1007/s10549-007-9706-5.
41. Galipeau N, Klooster B, Krohe M, Tang DH, Revicki DA, Cella D. Understanding key symptoms, side effects, and impacts of HR+/HER2- advanced breast cancer: qualitative study findings. *J Patient Rep Outcomes*. 2019;3:10. https://doi.org/10.1186/s41687-019-0098-1.
42. Reed E, Simmonds P, Haviland J, Corner J. Quality of life and experience of care in women with metastatic breast cancer: a cross-sectional survey. *J Pain Symptom Manage*. 2012;43(4):747–758. https://doi.org/10.1016/j.jpainsymman.2011.05.005.

43. Girgis A, Lambert S, Johnson C, Waller A, Currow D. Physical, Psychosocial, Relationship, and Economic Burden of Caring for People With Cancer: A Review. *JOP*. 2013;9(4):197–202. https://doi.org/10.1200/JOP.2012.000690.
44. Grunfeld E, Coyle D, Whelan T, *et al.* Family caregiver burden: results of a longitudinal study of breast cancer patients and their principal caregivers. *CMAJ*. 2004;170(12):1795–1801. https://doi.org/10.1503/cmaj.1031205.
45. Breast Cancer Now. The cost of breast cancer: Modelling the economic impact to the UK. 2024. Last accessed: 02/16/2024. https://demos.co.uk/wp-content/uploads/2024/01/Cost-of-Breast-Cancer-Report.pdf.
46. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. *Br J Cancer*. 2006;95(6):683–690. https://doi.org/10.1038/sj.bjc.6603326.
47. Gennari A, André F, Barrios CH, *et al.* ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer☆. *Annals of Oncology*. 2021;32(12):1475–1495. https://doi.org/10.1016/j.annonc.2021.09.019.
48. Cardoso F, Kyriakides S, Ohno S, *et al.* Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol*. 2019;30(8):1194–1220. https://doi.org/10.1093/annonc/mdz173.
49. NICE. Early and locally advanced breast cancer: diagnosis and management NG101. National Institute for Health and Care Excellence; 2023.
50. NICE. Advanced breast cancer: diagnosis and treatment CG81. National Institute for Health and Care Excellence; 2017.
51. Gagan J, Van Allen EM. Next-generation sequencing to guide cancer therapy. *Genome Medicine*. 2015;7(1):80. https://doi.org/10.1186/s13073-015-0203-x.
52. Curigliano G, Castelo-Branco L, Gennari A, Harbeck N, Criscitiello C. ESMO Metastatic Breast Cancer Living Guideline > ER-positive HER2-negative Breast Cancer. 2023.
53. NICE. Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer: TA495. National Institute for Health and Care Excellence; 2017.
54. NICE. Ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer: TA496. National Institute for Health and Care Excellence; 2017.
55. NICE. Abemaciclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer: TA563. National Institute for Health and Care Excellence; 2019.
56. NICE. Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy: TA836. National Institute for Health and Care Excellence; 2022.
57. NICE. Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy: TA725. National Institute for Health and Care Excellence; 2021.
58. NICE. Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy: TA687. National Institute for Health and Care Excellence; 2021.
59. NICE. Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens: TA423. National Institute for Health and Care Excellence; 2016.
60. NICE. Gemcitabine for the treatment of metastatic breast cancer: TA116. National Institute for Health and Care Excellence; 2007.
61. Salas M, Mordin M, Castro C, Islam Z, Tu N, Hackshaw MD. Health-related quality of life in women with breast cancer: a review of measures. *BMC Cancer*. 2022;22:66. https://doi.org/10.1186/s12885-021-09157-w.
62. Kimman ML, Dirksen CD, Lambin P, Boersma LJ. Responsiveness of the EQ-5D in breast cancer patients in their first year after treatment. *Health and Quality of Life Outcomes*. 2009;7(1):11. https://doi.org/10.1186/1477-7525-7-11.
63. Wallwiener M, Simoes E, Sokolov AN, Brucker SY, Fasching PA, Graf J. Health-related Quality of Life in Metastatic and Adjuvant Breast Cancer Patients. *Geburtshilfe Frauenheilkd*. 2016;76(10):1065–1073. https://doi.org/10.1055/s-0042-113188.
64. Brady MJ, Cella DF, Mo F, *et al.* Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. *J Clin Oncol*. 1997;15(3):974–986. https://doi.org/10.1200/JCO.1997.15.3.974.

65. Fallowfield L, Starkings R, Palmieri C, *et al.* Living with metastatic breast cancer (LIMBER): experiences, quality of life, gaps in information, care and support of patients in the UK. *Support Care Cancer*. 2023;31(8):459. https://doi.org/10.1007/s00520-023-07928-8.
66. Meegdes M, Geurts SME, Erdkamp FLG, *et al.* Real-world time trends in overall survival, treatments and patient characteristics in HR+/HER2- metastatic breast cancer: an observational study of the SONABRE Registry. *Lancet Reg Health Eur*. 2023;26:100573. https://doi.org/10.1016/j.lanepe.2022.100573.
67. Yin W, Horblyuk R, Perkins JJ, *et al.* Association Between Breast Cancer Disease Progression and Workplace Productivity in the United States. *Journal of Occupational and Environmental Medicine*. 2017;59(2):198. https://doi.org/10.1097/JOM.0000000000000936.
68. Cardoso F, Rihani J, Harmer V, *et al.* Quality of Life and Treatment-Related Side Effects in Patients With HR+/HER2- Advanced Breast Cancer: Findings From a Multicountry Survey. *Oncologist*. 2023;28(10):856–865. https://doi.org/10.1093/oncolo/oyad207.
69. Menarini Stemline. Clinical Study Report v.2: Elacestrant monotherapy vs. standard of care for the treatment of patients with ER+/HER2- advanced breast cancer following CDK4/6 inhibitor therapy: A phase 3 randomized, open-label, active-controlled, multicenter trial (EMERALD). 2023.
70. Bidard F-C, Kaklamani VG, Neven P, *et al.* Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. *J Clin Oncol*. 2022;40(28):3246–3256. https://doi.org/10.1200/JCO.22.00338.
71. Bardia A, Aftimos P, Bihani T, *et al.* EMERALD: Phase III trial of elacestrant (RAD1901) vs endocrine therapy for previously treated ER+ advanced breast cancer. *Future Oncology*. 2019;15(28):3209–3218. https://doi.org/10.2217/fon-2019-0370.
72. Menarini Stemline. ORSERDU (elacestrant) - prescribing information. .
73. Reinert T, Saad ED, Barrios CH, Bines J. Clinical Implications of *ESR1* Mutations in Hormone Receptor-Positive Advanced Breast Cancer. *Front Oncol*. 2017;7:26. https://doi.org/10.3389/fonc.2017.00026.
74. Stemline Therapeutics. Package leaflet: Information for the patient: KORSERDU 86 mg film-coated tablets and KORSERDU 345 mg film-coated tablets (elacestrant). 2023.
75. Menarini Stemline. EMERALD Data on File: UK Requests, CDK4/6 12 month plus data for *ESR1* mutation population. .
76. Menarini Stemline. Overall Survival Addendum to Clinical Study Report v.2 RAD1901-308 | Elacestrant monotherapy vs. standard of care for the treatment of patients with ER+/HER2- advanced breast cancer following CDK4/6 inhibitor therapy: a Phase 3 randomized, open-label, active-controlled, multicenter trial (EMERALD) | overall survival addendum as of 2nd September 2022. 2023.
77. Menarini Stemline. EMERALD Data on File: UK Requests, CDK4/6 12 month plus data for dual mutation population (*ESR1* + *PIK3CA*). .
78. European Medicines Agency. Assessment report: Orserdu. International non-proprietary name: elacestrant. Procedure No. EMEA/H/C/005898/0000. .
79. Cortés J, Bidard FC, Bardia A, *et al.* 188O EMERALD trial analysis of patient-reported outcomes (PROs) in patients with ER+/HER2− advanced or metastatic breast cancer (mBC) comparing oral elacestrant vs standard of care (SOC) endocrine therapy. *ESMO Open*. 2023;8(1):101377. https://doi.org/10.1016/j.esmoop.2023.101377.
80. Fallowfield L, Atkins L, Catt S, *et al.* Patients' preference for administration of endocrine treatments by injection or tablets: results from a study of women with breast cancer. *Ann Oncol*. 2006;17(2):205–210. https://doi.org/10.1093/annonc/mdj044.
81. Mittal A, Molto Valiente C, Tamimi F, *et al.* Filling the Gap after CDK4/6 Inhibitors: Novel Endocrine and Biologic Treatment Options for Metastatic Hormone Receptor Positive Breast Cancer. *Cancers (Basel)*. 2023;15(7):2015. https://doi.org/10.3390/cancers15072015.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Company response to clarification questions

May 2024

File name	Version	Contains confidential information	Date
ID6225_Elacestrant-ESR1-mutated-aBC_Company-response-to-clarifications [redacted]	1.0	No	30 May 2024

Section A: Clarification on effectiveness data

References

A1. In the company-supplied zip folder, "**ID6225 elacestrant Reference Pack folder 6 of 7 Unpublished 190424 [CON]**", there are [redacted]. Please confirm which references in CS document B each of these documents refer to.

Response: Thank you for drawing our attention to this. We have reviewed the relevant folders and identified that, alongside the correct reference file, some additional files were uploaded. We have uploaded a revised reference pack to NICE Docs alongside this response document. This new zip file replaces the previous one in its entirety.

We have renamed the relevant files from the three subfolders mentioned in this query to better match the document reference, and these now replace the original three subfolders. New document titles are below:

- '*MS_EMERALD-DoF_UK-req_CDK46-12-month-plus-ESR1-m*'
- '*MS_EMERALD-DoF_UK-req_CDK46_12-month-plus-dual-mut*'
- '*MS_EMERALD-DoF_UK-req_add-all-ESR1-m-PRO*'

Please also note that the text highlighted blue in the EAG question above is not confidential and can be unredacted.

A2. CS, Document B, References, p184. Please confirm whether the documents relating to references 100, 101 and 102 in CS document B have been provided. If so, please provide the documents' file names.

Response: References 100 (*Menarini Stemline. EMERALD Data on File: UK Requests, CDK4/6 12 month plus data for ESR1 mutation population*) and 101 (*Menarini Stemline. EMERALD Data on File: UK Requests, CDK4/6 12 month plus data for dual mutation population (ESR1 + PIK3CA*) relate to the query in question A1 above. Reference 102 was also originally provided in the folder title '*ID6225_Elacestrant-ESR1-mutated-aBC_Reference_Pack_folder_6_of_7_Unpublished'*. In response to this question we have renamed the relevant files to clarify which reference they relate to. In summary:

- Reference 100: Please see file titled '*MS_EMERALD-DoF_UK-req_CDK46-12-month-plus-ESR1-m*'
- Reference 101: Please see file titled '*MS_EMERALD-DoF_UK-req_CDK46_12-month-plus-dual-mut'*
- Reference 102: Please see file titled '*MS_DoF_OS-Addendum-CSR-v2.0-RAD1901-308_EMERALD'*

These files can now be found in the new zip folder titled '*ID6225_Elacestrant-ESR1-mutated-aBC_Reference_Pack_folder-6-of-7_Unpublished*' that we have sent alongside this document. All the relevant files have been copied across to the new folder.

Elacestrant clinical trial programme

A3. PRIORITY QUESTION: ID6225 elacestrant Reference Pack folder 7 of 7 Unpublished 190424 [CON] zipped folder. [redacted]. Please provide a list/summary of all elacestrant phase 1, phase 2 and phase 3 clinical trials.

Response: The statement in the CSR refers to the studies used for dose finding for the 400 mg QD dose of elacestrant used in the Phase 3 study. These six clinical studies included two Phase 1 studies in healthy postmenopausal volunteers and two Phase 1 studies in postmenopausal women with mBC. In addition, it also included two phase 2 studies for vasomotor symptoms, which was then not pursued as an indication.

Table 1 refers to the relevant clinical studies for elacestrant clinical pharmacology with, Table 2 including studies for elacestrant in mBC. Four of the six studies referred to in the CSR are included and highlighted in these tables. With regard to the two vasomotor studies, these have not been included as they are not relevant to the indication in the submission, but further information can be found at https://classic.clinicaltrials.gov/ct2/show/NCT02653417 and https://classic.clinicaltrials.gov/ct2/show/NCT00875420.

Table 1: Overview of the clinical studies relevant to elacestrant clinical pharmacology

Type	Number	Objectives	Key Design	Population Number of subjects	Treatment
Phase 1 Study					
Healthy subject pharmacokinetics studies	***RAD-1901-001/***	• ***Safety/tolerability*** • ***Single- and multiple-dose PK of elacestrant*** • ***Bioavailability*** • ***Ascending dose*** • ***Food effect***	***Single-ascending and Multiple-ascending dose PK***	***Postmenopausal women*** ***Healthy subjects N=80*** • ***SAD n=32 (24 elacestrant/8 placebo)*** • ***MAD: n=48 (38 elacestrant/10 placebo)***	***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***
Healthy subject pharmacokinetics studies	***RAD1901-004/***	• ***MTD*** • ***Safety/tolerability*** • ***PD of elacestrant*** • ***PK of elacestrant*** • ***Elacestrant CSF concentrations***	***Multiple-dose PK***	***Postmenopausal women Healthy subjects N=52 (44 elacestrant/8 placebo)***	• ***Elacestrant 200, 500, 750, and 1000 mg capsule or placebo QD for 7 days***
Extrinsic factor studies	RAD1901-109/	• Effect of food on elacestrant PK	Single-dose food effect	Postmenopausal women and men Healthy subjects N=18	• Elacestrant 400 mg tablet, single oral dose on Day 1 of each period
Extrinsic factor studies	RAD1901-110/	• Effect of strong CYP3A4 inhibitor itraconazole on elacestrant PK	DDI	Postmenopausal women and men Healthy subjects N=18	• Elacestrant 200 mg tablet QD for the first 7 days • Followed by elacestrant 200 mg tablet QD + itraconazole 200 mg

					capsule QD for the next 7 days
Healthy subject pharmacokinetics studies	RAD1901-111/	• Absorption • Metabolism • Distribution • Excretion of ^{14}C-elacestrant	ADME (mass balance)	Men Healthy subjects N=7	• ^{14}C-elacestrant 400 mg capsule, single oral dose
	RAD1901-112/	• Relative bioavailability (2 prototype tablets compared to clinical tablet) • Food effect	Relative bioavailability and food effect	Postmenopausal women and men Healthy subjects N=36 • Cohort 1: N=18 • Cohort 2: N=18	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
Extrinsic factor studies	RAD1901-113/	• Effect of strong CYP3A4 inducer rifampin on elacestrant PK	DDI	Postmenopausal women and men Healthy subjects N=18	• 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/	• Effect of highly protein-bound drugs warfarin and elacestrant on each other's PK	DDI	Postmenopausal women and men Healthy subjects N=18	• 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 + warfarin 25 mg (2×10 mg and 1×5 mg tablets), single oral dose on Day 1
Extrinsic factor studies	RAD1901-115/	• Effect of proton pump inhibitor omeprazole on elacestrant PK	DDI	Postmenopausal women and men Healthy subjects N=18	• 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
Special population	RAD1901-117/	• Effect of mild or moderate hepatic impairment on elacestrant PK	Nonrandomized, open-label, parallel-group, hepatic impairment	Women and men with mild and moderate hepatic impairment or healthy subjects N=36 • Normal hepatic function: N=16	• Elacestrant 200 mg (2×100 mg tablets), single oral dose

				• Mild hepatic impairment: N=10 • Moderate hepatic impairment: N=10	
Extrinsic factor studies	RAD1901-118/	• 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 • Cohort 2: Rosuvastatin: N=21	• 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

Source: EMA assessment report (EMA/CHMP/358130/2023)[1]

Abbreviations: ADME, Absorption, distribution, metabolism, and excretion; BCRP, breast cancer resistant protein; CSF, cerebrospinal fluid; CYP3A4; Cytochrome P450 3A4; DDI, drug–drug interaction; IV, intravenous(ly); MAD, multiple ascending dose; MTD, maximum tolerated dose; N, number; PD, pharmacodynamic(s); PK, pharmacokinetic(s); QD, once daily; SAD. single ascending dose;

Table 2: 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**	**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	Open-label, multisite, randomized, active-controlled, event-driven study	Elacestrant 400 mg QD PO SOC: • Fulvestrant 500 mg IM • Anastrozole 1 mg QD PO • Letrozole 2.5 mg QD PO • Exemestane 25 mg QD PO	478 subjects (228 ESR1-mut and 250 ESR1-mut-nd) 1:1 randomization to either elacestrant or SOC	Postmenopaus al 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)
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*	*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*	*16 subjects*	*Postmenopausal women with histologically-confirmed, ER+/HER2- mBC*	*Tumour response as assessed by the investigator using RECIST v1.1*

Source: EMA assessment report (EMA/CHMP/358130/2023)[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.

Meaningful changes in efficacy and safety

A4. **CS, Document B, section B.2.12.1.** In several places in the company submission, it is stated that changes in given efficacy outcomes were “meaningful”, and occasionally “clinically meaningful”. For example, “meaningful median OS advantage was seen in the dual mutated subgroup and benefit was seen across multiple analysis points” (CS, section B.2.12.1). Please define meaningful in this context, providing detail on any established minimum clinically important differences or other benchmark which informed the company’s judgement on how meaningful the results were.

Response: The company recognise that this should have been made clear in the submission. The term meaningful was not based on established clinically important differences but on whether the results were statistically significant or not. [redacted].

EQ-5D-5L Index score and EQ-VAS score

A5. PRIORITY QUESTION: CS, Document B, section B.2.6.4. CS, Appendices, section E.2.1.1. Please clarify why there are large differences between the number of patients in each arm of the EMERALD trial who have an EQ-5D-5L Index score compared to those who have an EQ-VAS score (CS Document B Table 18 and CS Appendices Table 9). For example, in Table 18, there were 115 patients in the ESR1 mut subgroup elacestrant arm of whom 50 patients had an EQ-5D-5L Index score compared to 108 who had an EQ-VAS score at baseline (please also see Question B3).

Response: The EQ-5D-5L overall score is derived from a validated tool that was used by the company’s biostatistics and clinical data management department, and is available for 10 countries worldwide. The EMERALD study included patients in five

of the countries where this validated tool is available, namely Denmark, Spain, France, Great Britain and the USA. It was therefore only possible to derive an overall score value for these countries; for all other patients in the other countries the overall score was set to missing. The rationale behind this approach followed by biostatistics is to have index values for countries coming from data collected in those countries.

The company was aware that this approach is not in line with the standard way EQ-5D values are scored in HTA, and that there now exists a range of validated algorithms to calculate EQ-5D-5L overall scores. Consequently, the analysis the company performed in its initial submission was conducted to score EQ-5D to utility making use of *all patients with an EQ-5D score* and applied a UK-specific algorithm for calculating the utility scores.[2] Importantly, this means that while the overall EQ-5D scores in the CS are based on a subset of the EQ-5D data collected in EMERALD, the economic model uses all the EQ-5D data collected, as per preferred NICE methodology.

EMERALD trial subgroup analyses

A6. CS, Document B, section B.2.7. CS, Appendices, section E.1. In section B.2.7, it states that pre-specified subgroup analyses were performed for IRC-assessed PFS, OS, ORR, DOR and CBR “unless the number of patients in the subgroup in each treatment group was not sufficiently large (e.g. <5%)”.

a) Please state the denominator used to calculate this percentage (i.e. all patients/all patients with ESR1-mut).

b) Please state the rationale for choosing 5% or less as the threshold, as opposed to other potential thresholds (e.g. 10%, 20%).

c) Please state which subgroup analyses were not performed because they were not considered sufficiently large (i.e. <5%). Please state the number of participants in each respective subgroup analysis (i.e. subgroup by outcome).

d) In Appendix E.1, it is stated that “due to the low absolute number of patients with an objective response (OR) or clinical benefit, the subgroup analyses of

ORR, DOR and CBR are not discussed or considered further". Please clarify whether this is related to the above 5% threshold for subgroup size, or based on a different criterion. If so, please provide details.

Response (a–d): The company notes that although it was stated in the SAP that "A subgroup analysis may not be performed if the number of subjects in the subgroup in each treatment group is not sufficiently large (e.g., <5%)", analyses were actually performed for all pre-specified subgroups, regardless of this 5% threshold. These analyses can be found in the appendices of the CSR provided.

A7. PRIORITY QUESTION: CS, Document B, section B.2.7.1. In section B.2.7.1, it states that several additional post-hoc subgroup analyses from the EMERALD trial were performed following the data cut of 6th September 2021. The EAG notes that only 2 such subgroup analyses are reported in the company submission (i.e. patients with an ESR1-mut who received ≥12 months of prior ET + CDK4/6i and patients with ESR1-mut, PIK3CA-mut who received ≥12 months of prior ET + CDK4/6i [dual mutated]).

a) **Please provide details of the other post-hoc subgroup analyses that were performed.**

Response: Please see below a list of the *post-hoc* subgroup analyses that have been performed and are in the public domain, alongside their corresponding publications.

- **Subgroup analysis looking at patients from EMERALD with no prior chemotherapy**
    - *Subgroup analysis of patients with no prior chemotherapy in EMERALD: a phase 3 trial evaluating elacestrant, an oral selective estrogen receptor degrader (SERD), vs investigator's*

choice of endocrine monotherapy for ER+/HER2- advanced/metastatic breast cancer (mBC).[3]

- **Subgroup analysis looking at elacestrant vs fulvestrant or aromatase inhibitor alone**
    - *Elacestrant versus fulvestrant or aromatase inhibitor (AI) in phase 3 trial evaluating elacestrant, an oral selective estrogen receptor degrader (SERD) vs standard of care (SOC) endocrine monotherapy for ER+/HER2- advanced/metastatic breast cancer (mBC): Subgroup analysis from EMERALD*.[4]

- **Subgroup analysis looking at prior duration of CDK4/6i in the metastatic setting**
    - Poster presented at the 2022 San Antonio Breast Cancer Symposium (SABCS). December 8, 2022 | *GS3-01 EMERALD phase 3 trial of elacestrant versus standard of care endocrine therapy in patients with ER+/HER2- metastatic breast cancer: Updated results by duration of prior CDK4/6i in metastatic setting*. Abstract GS3-01[5,6]

- **Subgroup analysis looking at prior duration of CDK4/6i and ET in patients from EMERALD with non-detectable ESR1 mutation**
    - Poster presented at 2023 ASCO. June 04, 2023 | *EMERALD: Oral elacestrant vs standard-of-care in estrogen receptor-positive, HER2-negative (ER+/HER2-) advanced or metastatic breast cancer (mBC) with non-detectable ESR1 mutation (EMERALD): subgroup analysis by prior duration of CDK4/6i plus endocrine therapy (ET).*[7,8]

- **Subgroup analysis of EMERALD data based on key biomarkers, including patients with dual mutations in ESR1 and PIK3CA**
    - Poster presented at SABCS, December 5-9, 2023; Abstract PS17-02 | *Elacestrant vs standard-of-care in ER+/HER2- advanced or metastatic breast cancer (mBC) with ESR1*

mutation: key biomarkers and clinical subgroup analyses from the phase 3 EMERALD trial.[9,10]

b) Please describe the process/criteria which resulted in the selection of the 2 aforementioned post-hoc subgroups out of the several subgroup analyses performed. In particular, please describe the clinical rationale for the 2 selected subgroups.

Response: A crucial part of determining the appropriate treatment sequence in patients with advanced/mBC breast cancer is identifying patients' sensitivity to ET. Current definitions of 'endocrine resistance' were developed before CDK4/6i became a standard frontline treatment:[11]

- Primary endocrine resistance in the metastatic setting: progressive disease within the first 6 months of first line ET.
- Secondary (acquired) resistance: PD ≥ 6 months after initiating ET for MBC, while on ET.

However, the addition of CDK4/6i to ET has led to prolonged treatment duration and a significant improvement in survival for patients with mBC (median duration of treatment for first line CDK4/6i + ET is 18-21 months).[12–17] This prolonged PFS is reflected in the ESMO Breast cancer living guidelines when choosing subsequent treatments, where additional endocrine-based treatments are recommended for patients who experience a long PFS on previous CDK4/6i + ET (if there is no BRCA/PALB2 mutation).[18]

As the ESMO guidelines do not specify what qualifies as 'long PFS', the company engaged extensively with UK clinical experts to better understand appropriate cut-offs for ET in determining subsequent treatment decisions.

According to UK clinical feedback, in the post-CDK4/6i era, while patients who progress within 6 months of CDK4/6i are considered to have primary endocrine resistance and are unlikely to benefit from further endocrine treatment, there is

still uncertainty for patients who progress between 6 and 12 months. In these patients, other factors need to be considered when deciding further treatment, including presentation and disease biology. Patients who progress after at least 12 months of CDK4/6i are deemed endocrine sensitive (as long as ESR1-mediated, acquired resistance is overcome) and would benefit from further endocrine treatment.

As EMERALD mandated prior CDK4/6i use for all patients and allowed enrolment of patients with primary endocrine resistance, it provided the opportunity to analyse prior ET+ CDK4/6i duration as a potential surrogate marker for endocrine sensitivity and elacestrant efficacy.[5] Three subgroups were analysed; patients with at least 6 months, 12 months or 18 months of prior CDK4/6i + ET. Longer duration on CDK4/6i was associated with improvement in PFS for patients treated with elacestrant in the EMERALD trial. This was more pronounced in patients with at least 12 and 18 months of prior CDK4/6i duration. The company presented these data to clinicians at the San Antonio Breast Cancer Symposium, and clinicians confirmed that the subgroup of patients with ER+/HER2-, locally advanced/mBC with an ESR1 mutation who have disease progression following ≥12 months of prior treatment with ET + CDK4/6i, was where they perceived elacestrant would provide the most value in UK clinical practice and was therefore reported in this submission.

After progression with ET + CDK4/6i, NICE recommends treatment with alpelisib + fulvestrant in patients with a PIK3CA-mutated tumour. As PIK3CA and ESR1 mutations can co-exist (dual-mutated population),[9] alpelisib + fulvestrant is considered a comparator for elacestrant in this dual-mutated population. Therefore, the subgroup of patients with ESR1-mut and PIK3CA-mut who received ≥12 months of prior ET + CDK4/6 was reported in this submission to enable this comparison. Clinical experts have confirmed to the company that the same considerations regarding prior ET exposure (i.e. ≥12 months) apply for this population.

Please note that one of the references supplied in the original reference pack ("ID6225_Elacestrant-ESR1-mutated-aBC_Reference_Pack_folder_1-of-7") was

incorrect (Bardia_2023_PS17-02' poster).[9] The correct reference has been supplied alongside this response.

c) **Please clarify the choice of ≥12 months of prior ET + CDK4/6i as the threshold for inclusion in the 2 aforementioned subgroups, as opposed to other potential thresholds for duration of prior ET + CDK4/6i.**

Response: Please see response (b) above.

A8. CS, Document B and Appendices. In several places in Document B, the efficacy results for the 2 post-hoc subgroups are described as "consistent with those reported for All Patients", usually with a cross-reference to a different section of Document B or appendices.

However, the EAG are unable to find efficacy results for All patients in Document B or Appendices. For transparency, completeness and for purposes of comparison, please provide results for All Patients for all efficacy and safety analyses.

Response: Thank you for your question. To clarify we have identified cross-references as indicated by the EAG in six locations in Document B (pages 32, 76, 80 and 100) and four locations in the Appendices (pages 27, 31, 34 and 37).

To confirm the company's approach to presenting data on clinical effectiveness for elacestrant, the CS provides efficacy data (CS, Section B.2.6) and safety data (CS, Section B.2.10) for 'all patients with ESR1-mut' from the EMERALD trial. This is per the GB Marketing Authorisation for elacestrant and is consistent with the population within the scope of this appraisal. In addition, the CS also includes safety data for '*All Patients*', i.e. including patients without *ESR1* mutations (CS, Section B.2.10).

Where there is discussion of consistency of subgroup data compared with 'All Patients' (i.e. for patients without *ESR1* mutations), this is specifically for HRQoL and safety only, as follows:

- Section B.2.6.4 (pg 64) in the CS states that 'QoL was maintained between treatment groups in the EMERALD trial and over time, and results were similar to those for All Patients.' This statement is corroborated by reference 114 in Document B (*European Medicines Agency. Assessment report: Orserdu. International non-proprietary name: elacestrant. Procedure No. EMEA/H/C/005898/0000*)[1] and reference 109 in Document B (*Cortés J, Bidard FC, Bardia A, et al. 188O EMERALD trial analysis of patient-reported outcomes (PROs) in patients with ER+/HER2− advanced or metastatic breast cancer (mBC) comparing oral elacestrant vs standard of care (SOC) endocrine therapy. ESMO Open. 2023;8(1):101377*).[19]

- For HRQoL, data for 'All Patients' are available in reference 98 in Document B (*Menarini Stemline. Clinical Study Report v.2: Elacestrant monotherapy vs. standard of care for the treatment of patients with ER+/HER2- advanced breast cancer following CDK4/6 inhibitor therapy: A phase 3 randomized, open-label, active-controlled, multicenter trial (EMERALD). 2023*).[20]

A9. CS, Document B, sections B.2.7.2 and B.2.7.3. The efficacy results reported for the 2 post-hoc subgroups comprise PFS, OS, health-related quality of life and safety. However, this is not the complete set of outcome measures from the EMERALD trial. For example, response rates are omitted. Please provide results for the 2 post-hoc subgroups for all efficacy and safety outcomes.

Response: The requested subgroup data for overall response rate (ORR), clinical benefit rate (CBR) and duration of response have been provided in a separate, confidential Excel file, titled "*MS_EMERALD-DoF_UK-req_ORR_CBR_DoR*". These data have been provided as commercial in confidence.

A10. CS, Appendices, section E. Sections E.2.1.2 and E.3.1.2 (EORTC QLQ-C30) and sections E.2.1.3 and E.3.1.3 (PRO-CTCAE) report change from baseline scores for the respective post-hoc subgroups. However, they do not provide absolute values

at baseline, end of treatment, follow-up and at assessment time points in between for these outcome measures. Please provide these data.

Response: The requested subgroup data have been provided in a separate, confidential Excel file, titled "*MS_EMERALD-DoF_UK-req_EORTC QLQ-C30 PRO-CTCAE_All timepoints*". These data have been provided as commercial in confidence.

Matched adjusted indirect comparison (MAIC)

A11. CS, Document B, section B.2.9. Please clarify whether any other real world evidence sources outside the UK and Europe were considered besides the Flatiron database. If so, please summarise the selection process.

Response:

Criteria for selecting real-world data sources

The selection of RWE sources was driven by specific criteria crucial for ensuring the robustness and relevance of the MAIC analysis:

1. Capture of *ESR1*-mutations:

   The primary criterion was the detailed and accurate documentation of *ESR1*-mutations. These mutations are pivotal in assessing resistance to endocrine therapy in hormone receptor-positive, HER2-negative metastatic breast cancer, which is central to the comparative effectiveness analysis of elacestrant vs. everolimus + exemestane in the MAIC. No European datasets with this granularity were identified, thus a targeted literature review was conducted for genomic information in electronic health record real-world data sources from the United States (US).

2. Sample size and data quality:

The chosen data source needed to provide a sufficiently large sample size to ensure statistical validity and robustness. Additionally, the quality of the data, including the accuracy of mutation documentation and treatment records, was essential.

3. Regulatory/HTA acceptability and ethical compliance:

   Ensuring compliance with all relevant data protection regulations and ethical standards was a prerequisite for any data source considered. Data sources were shortlisted based on positive acceptability of respective real-world evidence in the regulatory as well as HTA context.

Evaluation of shortlisted real-world data sources

Two major US-based real-world databases were evaluated for their suitability, which included a personal reach-out and dataset feasibility request.

Patient360 Breast from ConcertAI[21]: Although this database also contained relevant data, it had a smaller sample size (Table 3) compared to Flatiron, particularly in the context of patients with documented *ESR1*-mutations and specific treatment regimens.

Table 3: Patient360 Breast (ConcertAI) database patient numbers

Patient360 Breast (ConcertAI)	N
Number of patients with advanced mBC	[redacted]
ER+/HER2-	[redacted]
ESR1+	[redacted]
Up to two lines of ET* and additional CDK4/6 inhibitor exposure**	[redacted]
Received everolimus and exemestane in their next line of therapy	[redacted]
ESR1-mut positive before or max 4 weeks after the start of treatment	[redacted]

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER+, oestrogen receptor positive; ESR1, oestrogen receptor 1 gene; ET, endocrine therapy; HER2-; Human epidermal factor receptor 2-negative; mBC, metastatic breast cancer; N, number.
Note: * aromatase inhibitors, tamoxifen, fulvestrant, ospemertronate; **ribociclib, palbociclib, abemaciclib

Flatiron Health Clinico-Genomic Database (CGDB)[22]: This database was selected based on *ESR1*-mutation data and larger sample size (Table 4). It also included detailed patient treatment records and outcomes.

Table 4: Flatiron Health CGDB patient numbers

CGDB (Flatiron)	N
Included in June 2023 mBC CGDB	[redacted]
Of 1, ER+/HER2-	[redacted]
Of 2, Received ET* in 1L and/or 2L	[redacted]
Of 3, Received a CDK4/6 inhibitor** in 1L and/or 2L	[redacted]
Received everolimus and exemestane in 2L or 3L	[redacted]
Tested positive for *ESR1*-mutation before or within 28 days after the start of index line (reported date)	[redacted]

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CGDB, Clinico-Genomic Database; ER+, oestrogen receptor positive; ESR1, oestrogen receptor 1 gene; ET, endocrine therapy; HER2-; Human epidermal factor receptor 2-negative; mBC, metastatic breast cancer; N, number.
Note: *anastrozole, exemestane, letrozole, tamoxifen, fulvestrant, ospemifene; **ribociclib, palbociclib, abemaciclib

Differences in the attrition tables between the two datasets can be attributed to the distinct data formats and curation methods used for specific variables within each dataset. Additionally, an iterative process was employed to understand the sensitivity of various time windows, which helped in estimating the target sample size.

Decision Rationale

The Flatiron Health Database was selected for the ITC due to the larger cohort of patients fitting the specific inclusion criteria relevant to this study. In particular, the amount of *ESR1*-mutated patients who received everolimus and exemestane in 2L or 3L. The robustness of the Flatiron database combined with its regulatory-grade quality and proven acceptability was found to have a more reliable foundation for the planned MAIC analysis.

Conclusion

The selection of the clinico-genomic database from Flatiron Health was based on its comprehensive and well-accepted data at a time where information on *ESR1*-mutation testing and related mutations were still very rarely captured. Of the limited real-world data sources including data on *ESR1*-mutations identified, the larger cohort of patients meeting the specific treatment criteria essential for the robustness of the MAIC was selected. This decision is aligned with the core principles outlined in the NICE real-world evidence framework, ensuring the generation of high-quality and trusted evidence.

A12. CS, Document B, section B.2.9.1. Please clarify whether any methodological guidelines were used to inform the design and methods of the MAIC. If so, please cite these and state how they have been applied in the company submission.

Response: The MAIC followed the guidance regarding population-adjusted indirect comparisons set out in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18.[23]

Though TSD 18 primarily refers to comparisons based on randomized trials, the methodological guidelines were considered to remain relevant when applied to observational data. In particular, the comparator data obtained from Flatiron were selected by applying the patient eligibility criteria of the clinical trial EMERALD and the EMA label. Specifically, the Flatiron data attempted to capture 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 either one or two lines of endocrine therapy including a CDK 4/6 inhibitor.

A13. CS, Document B, section B.2.9. Please provide the programming code and the study data used for the MAIC.

Response: The programming code used for the MAIC analyses (produced in R) is provided in the Appendix. It is not possible to share the study data as these data are confidential. However, summary baseline characteristics and KM curves for the OS and PFS endpoints are provided in CS, Document B, Section B.2.9.

Section B: Clarification on cost-effectiveness data

Baseline patient characteristics

B1. CS, Document B, Tables 39, 76 and 79. CS, Economic model. There is a discrepancy between the mean age at baseline for the *ESR1-mut* and ≥12 months of prior ET + CDK4/6i subgroup as cited in Table 39 ([redacted] years), and the value used in the economic model ([redacted] years; also in CS, Tables 76 and 79). Please confirm the correct value.

Response: Thank you for highlighting this discrepancy. The value cited in CS Table 39 ([redacted] years) is correct. The value in the economic model and CS Tables 76 and 79 has been updated in the revised CS post-clarification questions.

B2. CS, Document B, Tables 26, 28 and 39. Please consider whether the mean age at baseline used in the economic model should reflect the MAIC-weighted data (as reported in Tables 26 and 28), rather than the unadjusted trial data (as in Table 39).

Response: The company notes the MAIC-weighted age at baseline could have been used to inform the economic model, though this was anticipated to have minimal impact on the cost-effectiveness results. For completeness, the company has performed a scenario analysis using the MAIC-weighted age at baseline, which is presented below in Table 5 (for details, please see company post-clarification model, Clarification Qs sheet).

Table 5: Scenario results - MAIC-adjusted age – Fixed PAS price

Scenario	Value	ICER (£/QALY)	NMB (£30,000 WTP)
ESR1-mut and ≥12 months of prior ET + CDK4/6i*			
EMERALD age at baseline	[redacted]	£24,868	£3,893
MAIC-adjusted age at baseline	[redacted]	£24,927	£3,837
ESR1-mut, PIK3CA-mut and ≥12 months of prior ET + CDK4/6i			
EMERALD age at baseline	[redacted]	Dominant	£20,451

MAIC-adjusted age at baseline	[redacted]	Dominant	£20,450

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ESR1, oestrogen receptor 1 gene; ET, endocrine therapy; ICER, incremental cost-effectiveness ratio; MAIC, matching-adjusted indirect comparison; NMB, net monetary benefit; PAS, patient access scheme; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; QALYs, quality-adjusted life years; WTP, willingness to pay.
Note: *A severity modifier of 1.2 is applied to the discounted incremental QALYs. **The original CS used an age of [redacted] which has been corrected to [redacted] in response to clarification question B1.

Health state utilities

B3. PRIORITY QUESTION: CS, Appendices, section E.2.1.1. Table 9 shows that there were high proportions of missing EQ-5D-5L index score data at baseline and end of treatment from the EMERALD trial. Please discuss whether and how this missing data might have biased the results of the health state regression model (please also see Question A5).

Response: Please see responses to Clarification Questions A5 and B4. The level of missing data in the utility analyses used to inform the model is described in response to B4.

B4. PRIORITY QUESTION: CS, Document B, section B.3.4.2. Please provide further details about the statistical methods used to fit the linear mixed-effects regression model that was used to estimate health state utility values for the economic model. In particular, please describe what methods were used to handle missing data, and how covariates included in the regression model were selected. Please report the full regression model results including coefficient values, measures of variance and significance and measures of model fit.

Response:

Missing data

Data for a total of 222 patients (elacestrant: N=112 and SOC: N=110) were included in the data preparation stage. However, 35 patients were excluded from the utility

analysis owing to the reasons presented in Table 6. After completion of data processing, a total of 187 patients with 886 EQ-5D-5L observations were included in the analytical dataset.

Table 6: EQ-5D-5L analysis – patient exclusions

Reason for exclusion	Number of patients
No EQ-5D-5L data available	4
Missing EQ-5D-5L domain scores	8
No baseline observation	8
Baseline observation available, no subsequent observations	4
All EQ-5D-5L observations occurring after date of progression censor	10
Missing covariate data	1
Total excluded	**35**

Abbreviations: EQ-5D, European Quality of Life Five Dimension.

Covariates

The covariates included in the regression model were considered to be potential prognostic and predictive of quality of life outcomes, and were selected based on a review of previous NICE Technology Appraisals (TAs).[24–29] A summary of the factors included in the regression model is presented in Table 7.

Table 7: Prognostic factors including in the utility regression model

Variable	Measure	Categorisation	Definition
Baseline age	Fixed	Continuous	Change in EQ-5D with each additional year of age
Baseline utility	Fixed	Continuous	Change in EQ-5D with each additional unit of baseline utility
Number of prior lines of therapy	Fixed	Second-line versus Third line onwards	Equal to 1 if an individual has received two or more prior lines of anti-cancer therapy in a metastatic setting (i.e. third line), and 0 otherwise
Adverse events	Time-varying	Yes versus No	Equal to 1 if an individual has a grade 3 or 4 AE ongoing at the time of the EQ-5D assessment, and 0 otherwise
Progression status	Time-varying	PD versus PF	Equal to 1 if an individual has PD at the time of the EQ-5D assessment, and 0 otherwise

Abbreviations: AE, adverse event; EQ-5D, European Quality of Life Five Dimension; PD, progressive disease; PF, progression-free.

Note, treatment arm was also identified for potential inclusion in the model, however, it was anticipated that occurrence of adverse events (AEs) and treatment arm were likely to be correlated and it was not expected that treatment arm would have a

statistically significant impact on patient's quality of life (supported by findings from a univariate model). Therefore, treatment arm was not included as a model covariate.

Methods

Patient records were considered progression-free (PF) if the date of the EQ-5D-5L assessment occurred prior to the date of progression or censoring for each patient. EQ-5D-5L assessments occurring after the date of progression (for patients with documented progression) were associated with a response of progressed disease (PD). Where a patient had no documented progression (i.e. censored for progression), all measurements were associated with a response of PF until the date of censoring; any records with questionnaires completed after the date of censoring were excluded from the HRQoL regression analysis (as progression status could not be determined).

A linear mixed-effects regression model was fitted to the data to reflect multiple observations per patient and the longitudinal structure of the data. All prognostic factors summarised in Table 7 were selected for inclusion in the model and were added as fixed-effects, with patient ID controlled for as a random-effect term. Baseline utility scores were included as a predictor variable to consider individual differences at baseline. Age and lines of prior anti-cancer therapy in a metastatic setting were also considered to be important factors and were included in the regression model. The occurrence of grade 3 or 4 AEs was included in the regression model (as an alternative to treatment arm) to estimate a corresponding utility decrement. Disutilities associated with AE occurrence are not included in the base case analysis to avoid double-counting, as the impact on health-related quality of life is assumed to be accounted for within the utility analysis. Finally, progression status was included to determine whether there is a statistically significant difference in utility values between health states.

Results

A summary of the utility regression model coefficients, standard errors and p-values are presented in Table 8.

Table 8: Utility regression model parameter estimates

	Coefficient	SE	p-value
Intercept	[redacted]	[redacted]	**0.0008**
Baseline utility score	[redacted]	[redacted]	**<0.0001**
Age (years)	[redacted]	[redacted]	**0.0289**
Number of prior LOT: 2+	[redacted]	[redacted]	0.5740
Grade 3/4 AE: Yes	[redacted]	[redacted]	**0.0010**
Progression status: PD	[redacted]	[redacted]	**0.0046**

Abbreviations: AE, adverse event; LOT, lines of therapy; PD, progressed disease; SE, standard error.

Goodness-of-fit

Model goodness-of-fit was assessed by inspection of diagnostic plots, including standardised residuals versus predicted values to help assess the linearity assumption, and quantile-quantile (QQ) plots as a test of normality. The model diagnostic plots are presented in Figure 1.

Figure 1: Utility regression model diagnostic plots

[redacted]

Adverse events

B5. CS, Document B, section B.3.4.4. There appears to be an error in the Telford et al. (2019) citation in Table 64: reference number 126 does not include the stated values. Please confirm whether the correct citation should be: "*Telford C, Bertranou E, Large S et al. Cost-Effectiveness Analysis of Fulvestrant 500 mg in Endocrine Therapy-Naïve Postmenopausal Women with Hormone Receptor-Positive Advanced Breast Cancer in the UK. Pharmacoecon Open. 2019 Dec;3(4):559-570. doi: 10.1007/s41669-019-0134-3.*" If not, please provide the correct citation.

Response: Thank you for highlighting this discrepancy. The correct citation is "*Telford C, Bertranou E, Large S et al. Cost-Effectiveness Analysis of Fulvestrant 500 mg in Endocrine Therapy-Naïve Postmenopausal Women with Hormone Receptor-Positive Advanced Breast Cancer in the UK. Pharmacoecon Open. 2019 Dec;3(4):559-570. doi: 10.1007/s41669-019-0134-3.*".[30] This has been corrected in the post-clarification questions CS.

B6. CS, Document B, section B.3.4.4. Please address the following questions related to adverse event (AE) disutilities in Table 64:

a) Please provide the correct source for the anaemia disutility value and duration: Telford *et al.* Pharmacoecon Open. 2019 Dec;3(4):559-570 does not provide this information.

Response: Thank you for highlighting this discrepancy. The disutility associated with anaemia was sourced from Swinburn *et al.* (2010).[31] Due to a lack of evidence identified from the literature, the duration of anaemia was assumed to be 1 model cycle. The source has been corrected in the updated economic model and post-clarification questions CS.

b) Please explain why the disutility and duration for dyspnoea were not based on the information provided in Telford *et al.* 2019 Pharmacoecon Open. 2019 Dec;3(4):559-570 Supplementary Table 8, and was instead assumed to be the same as for ALT increase.

Response: Thank you for highlighting this discrepancy. The input for duration of dyspnoea has been revised to use data reported in Telford et al. (2019) in the updated economic model and CS.[30] This update has no impact on the base case results, as AE disutility values are not considered in the base case analysis (as noted in CS Section B.3.8.2 and in response to Clarification Question B4).

c) Please verify the hyperglycaemia disutility value. In Smith-Palmer et al. 2016 the disutility seems to be related to hypoglycaemia events, not hyperglycaemia events.

Response: Thank you for highlighting this discrepancy. The disutility for hyperglycaemia has been updated to take the average of -0.09 and -0.071 (reported in Smith-Palmer et al. [2016]) in the updated economic model and company submission.[32] This update has no impact on the base case results as AE disutility is not considered in the base case analysis.

d) There is a discrepancy between the disutility value for thrombocytopenia reported in the Tolley *et al.* 2013 paper and that cited in Table 64. Please explain this difference and correct if appropriate.

Response: Thank you for highlighting this discrepancy. The disutility for thrombocytopenia was rounded to two decimal places in the economic model (from -0.108 to -0.11).[33] This has been revised in the updated economic model and post-clarification questions CS. This update has no impact on the base case results as AE disutility is not considered in the base case analysis.

B7. CS, Document B, section B.3.4.4. Please verify the AE frequencies in Table 63 and the economic model. Some values are misplaced in the EVE+EXE column (from the “nausea” row onwards) and in the alpelisib column (from the ”pneumonitis” row onwards).

Response: Thank you for highlighting this discrepancy. This has been corrected in the updated economic model and post-clarification questions CS. This update has no

impact on the base case results as AE disutility is not considered in the base case analysis.

Costs

B8. ESR1 mutation test unit cost: Please state the source for the cost of digital polymerase chain reaction (dPCR) testing used to estimate the cost for ESR1-mut testing in the economic model (Costs!H84).

Response: The company has not yet received the confirmed cost of the dPCR test from NHS England. At this stage the cost has been based on feedback from clinical pathologists.

B9. Resource unit cost: Please clarify the resource unit cost for physiotherapy in CS, section B.3.5.2, Table 69. The average cost between bands 5 and 6 (PSSRU 2022, Table 8.2.1) seems higher (£48.50) than reported in the company submission (£45.50).

Response: Thank you for highlighting, this value has been corrected to £48.50 in the updated economic model and post-clarification questions CS. The correction has minimal impact on the cost-effectiveness results (please see company post-clarification model, Clarification Qs sheet for details).

B10. Drug unit cost: Please verify the unit drug cost for Paclitaxel 100 mg in CS, section B.3.5.4.2, Table 73. There is a small discrepancy between the value stated in the company submission (£11.79) and that in eMIT (£11.49).

Response: Thank you for highlighting, this value has been corrected to £11.49 in the updated economic model post-clarification questions CS. The correction has

minimal impact on the cost-effectiveness results (please see company post-clarification model, Clarification Qs sheet for details).

B11. Subsequent treatment cost: There is a discrepancy between the subsequent treatment costs per treatment and total cost applied on progression as reported in CS, section B.3.5.4.2, Table 74 and the values in the economic model (Costs!P125:P127 and Costs!H147:M147, respectively). Please explain this difference and correct if appropriate.

Response: Thank you for highlighting this discrepancy. The values in the economic model are correct. The values in CS Tables 74 have been updated in the revised company submission post-clarification questions.

References

1. European Medicines Agency. Assessment report: Orserdu. International non-proprietary name: elacestrant. Procedure No. EMEA/H/C/005898/0000. Report No.: EMA/CHMP/358130/2023.

2. Devlin N, Shah K, Feng Y, Mulhern B, van Hout B. Valuing Health-Related Quality of Life: An EQ-5D-5L Value Set for England - OHE [Internet]. OHE - Leading intellectual authority on global health economics. 2016 [cited 2024 May 29]. Available from: https://www.ohe.org/publications/valuing-health-related-quality-life-eq-5d-5l-value-set-england/

3. Kaklamani VG, Bardia A, Aftimos PG, Cortes J, Lu JM, Neven P, et al. Subgroup analysis of patients with no prior chemotherapy in EMERALD: A phase 3 trial evaluating elacestrant, an oral selective estrogen receptor degrader (SERD), versus investigator's choice of endocrine monotherapy for ER+/HER2-advanced/metastatic breast cancer (mBC). Poster presented at ASCO congress 2022. Chicago, IL, USA. 3-8 June. In 2022.

4. Aftimos PG, Cortés J, Bidard FC, Kaklamani V, Bardia A, Neven P, et al. Elacestrant versus fulvestrant or aromatase inhibitor in phase 3 trial evaluating elacestrant, an oral selective estrogen receptor degrader versus standard of care endocrine monotherapy for ER+/HER2- advanced/metastatic breast cancer: Subgroup analysis from EMERALD. Oral presentation at at ESMO congress 2022. Paris, France. 09-13 September. In 2022.

5. Bardia A, Bidard FC, Neven P, Streich G, Montero AJ, Forget F, et al. EMERALD phase 3 trial of elacestrant versus standard of care endocrine therapy in patients with ER+/HER2- metastatic breast cancer: Updated results by duration of prior CDK4/6i in metastatic setting. Oral presentation at SABCS congress. San Antonio, TX, USA. 6-10 December. In 2022.

6. Bardia A, Bidard FC, Neven P, Streich G, Montero AJ, Forget F, et al. Abstract GS3-01: GS3-01 EMERALD phase 3 trial of elacestrant versus standard of care endocrine therapy in patients with ER+/HER2- metastatic breast cancer: Updated results by duration of prior CDK4/6i in metastatic setting. Cancer Research. 2023 Mar 1;83(5_Supplement):GS3-01.

7. Kaklamani V, Bidard FC, Neven P, Montero AJ, Mouret Reynier MA, Sohn JH, et al. Oral elacestrant vs standard-of-care in estrogen receptor-positive, HER2-negative (ER+/HER2-) advanced or metastatic breast cancer (mBC) with non-detectable ESR1 mutation (EMERALD): subgroup analysis by prior duration of CDK4/6i plus endocrine therapy (ET). Poster presented at ASCO Annual Meeting. Chicago, IL, USA. 2-6 June. In 2023.

8. Kaklamani VG, Bidard FC, Neven P, Montero AJ, Mouret-Reynier MA, Sohn J, et al. Oral elacestrant vs standard-of-care in estrogen receptor-positive, HER2-negative (ER+/HER2-) advanced or metastatic breast cancer (mBC) without detectable ESR1 mutation (EMERALD): Subgroup analysis by prior duration of CDK4/6i plus endocrine therapy (ET). JCO. 2023 Jun;41(16_suppl):1070–1070.

9. Bardia A, O'Shaughnessy J, Bidard FC, Neven P, Garcia-Saenz J, Aftimos P, et al. PS17-02 Elacestrant vs standard-of-care in ER+/HER2- advanced or metastatic breast cancer (mBC) with *ESR1* mutation: key biomarkers and clinical subgroup analyses from the phase 3 EMERALD trial. Poster presented at SABCS congress. San Antonio, TX, USA. 5-9 December. In: SABCS. 2023.

10. Bardia A, O'Shaughnessy J, Bidard FC, Neven P, García-Sáenz JÁ, Aftimos P, et al. Abstract PS17-02: Elacestrant vs standard-of-care in ER+/HER2- advanced or metastatic breast cancer (mBC) with ESR1 mutation: key biomarkers and clinical subgroup analyses from the phase 3 EMERALD trial. Cancer Research. 2024 May 2;84(9_Supplement):PS17-02.

11. Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, André F, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)†. Ann Oncol. 2018 Aug 1;29(8):1634–57.

12. Han Y, Wang J, Wang Z, Xu B. Comparative efficacy and safety of CDK4/6 and PI3K/AKT/mTOR inhibitors in women with hormone receptor-positive, HER2-negative metastatic breast cancer: a systematic review and network meta-analysis. Current Problems in Cancer. 2020 Dec 1;44(6):100606.

13. MHRA. Summary of Product Characteristics: IBRANCE 125 mg hard capsules [Internet]. [cited 2024 May 25] p. 29. Available from: https://mhraproducts4853.blob.core.windows.net/docs/a0e37fe1624c9cc0b8a503c7fffb8cf7fdae51c6

14. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. Annals of Oncology. 2018 Jul;29(7):1541–7.

15. Tripathy D, Im SA, Colleoni M, Franke F, Bardia A, Harbeck N, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. The Lancet Oncology. 2018 Jul 1;19(7):904–15.

16. Johnston S, Martin M, Di Leo A, Im SA, Awada A, Forrester T, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. NPJ Breast Cancer. 2019 Jan 17;5:5.

17. Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, et al. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med. 2016 Nov 17;375(20):1925–36.

18. Curigliano G, Castelo-Branco L, Gennari A, Harbeck N, Criscitiello C. ESMO Metastatic Breast Cancer Living Guideline > ER-positive HER2-negative Breast Cancer. 2023 May [cited 2023 Aug 11]; Available from: https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline/er-positive-her2-negative-breast-cancer

19. Cortés J, Bidard FC, Bardia A, Kaklamani VG, Vlachaki I, Tonini G, et al. 188O EMERALD trial analysis of patient-reported outcomes (PROs) in patients with ER+/HER2− advanced or metastatic breast cancer (mBC) comparing oral elacestrant vs standard of care (SOC) endocrine therapy. ESMO Open. 2023 May;8(1):101377.

20. Menarini Stemline. Clinical Study Report v.2: Elacestrant monotherapy vs. standard of care for the treatment of patients with ER+/HER2- advanced breast cancer following CDK4/6 inhibitor therapy: A phase 3 randomized, open-label, active-controlled, multicenter trial (EMERALD). 2023 Jan p. 4424.

21. ConcertAI. Real-World Data Products [Internet]. [cited 2024 May 28]. Available from: https://www.concertai.com/data-products

22. Flatiron. Clinico-Genomic Data is a Game Changer for Precision Oncology [Internet]. [cited 2024 May 28]. Available from: https://resources.flatiron.com/real-world-evidence/clinico-genomic-data-is-a-game-changer-for-precision-oncology/

23. Phillippo D. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submission to NICE [Internet]. 2022 [cited 2024 May 20]. Available from: https://www.sheffield.ac.uk/nice-dsu/tsds/population-adjusted

24. NICE. Alpelisib with fulvestrant for treating hormone receptor-positive, HER2-negative, *PIK3CA*-mutated advanced breast cancer: TA816 [Internet]. National Institute for Health and Care Excellence; 2022 Aug [cited 2023 Aug 11]. Available from: https://www.nice.org.uk/guidance/ta816

25. NICE. Fulvestrant for untreated locally advanced or metastatic oestrogen-receptor positive breast cancer: TA503. 2018.

26. NICE. Abemaciclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer: TA563 [Internet]. National Institute for Health and Care Excellence; 2019 Feb [cited 2023 Aug 11]. Available from: https://www.nice.org.uk/guidance/ta563

27. NICE. Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer: TA495. National Institute for Health and Care Excellence; 2017 Dec.

28. NICE. Ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer: TA496 [Internet]. National Institute for Health and Care Excellence; 2017 Dec [cited 2023 Aug 11]. Available from: https://www.nice.org.uk/guidance/ta496

29. NICE. Pertuzumab with trastuzumab and docetaxel for treating HER2-positive breast cancer: TA509 [Internet]. NICE; 2018 [cited 2024 May 28]. Available from: https://www.nice.org.uk/guidance/ta509

30. Telford C, Bertranou E, Large S, Phelps H, Ekman M, Livings C. Cost-Effectiveness Analysis of Fulvestrant 500 mg in Endocrine Therapy-Naïve Postmenopausal Women with Hormone Receptor-Positive Advanced Breast Cancer in the UK. Pharmacoecon Open. 2019 Apr 25;3(4):559–70.

31. Swinburn P, Lloyd A, Nathan P, Choueiri TK, Cella D, Neary MP. Elicitation of health state utilities in metastatic renal cell carcinoma. Curr Med Res Opin. 2010 May;26(5):1091–6.

32. Smith-Palmer J, Bae JP, Boye KS, Norrbacka K, Hunt B, Valentine WJ. Evaluating health-related quality of life in type 1 diabetes: a systematic literature review of utilities for adults with type 1 diabetes. Clinicoecon Outcomes Res. 2016;8:559–71.

33. Tolley K, Goad C, Yi Y, Maroudas P, Haiderali A, Thompson G. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. Eur J Health Econ. 2013 Oct;14(5):749–59.

Appendix

```
# Packages loading ----------------------------------

if(!require(dplyr)) {install.packages("dplyr",dependencies=TRUE); library(dplyr)}
if(!require(tidyr)) {install.packages("tidyr",dependencies=TRUE); library(tidyr)}
if(!require(wakefield)) {install.packages("wakefield",dependencies=TRUE); library(wakefield)}
if(!require(ggplot2)) {install.packages("ggplot2",dependencies=TRUE); library(ggplot2)}
if(!require(sandwich)) {install.packages("sandwich",dependencies=TRUE); library(sandwich)}
if(!require(readxl)) {install.packages("readxl",dependencies=TRUE); library(readxl)}
if(!require(survival)) {install.packages("readxl",dependencies=TRUE); library(survival)}
if(!require(ggsurvfit)) {install.packages("ggsurvfit",dependencies=TRUE); library(ggsurvfit)}
if(!require(gtsummary)) {install.packages("gtsummary",dependencies=TRUE); library(gtsummary)}
if(!require(survminer)) {install.packages("survminer",dependencies=TRUE); library(survminer)}

# Directory setting----------------------------------
# obtain automatically the path of the code
wd<-dirname(rstudioapi::getActiveDocumentContext()$path)
setwd(wd)
mytheme<-theme(plot.title=element_text(size=30,hjust=0.5),
               legend.text=element_text(size=28),
               axis.text.y=element_text(size=28),
               axis.title.y=element_text(size=30),
               axis.title.x=element_text(size=30),
               axis.text.x=element_text(size=28))

# create the path for the outputs (graphs)
Output_path="./MAIC_output/"

# Data loading & management ------------------------------------
# Population 2 - ESR1-mut and ≥12 months of prior ET + CDK4/6i population
dataIPD_pop2<-read_excel("../02 - Data for analysis/EMERALD/Population
2/original_ipd_pop2_elacestrant.xlsx")
dataAGD_pop2<-read_excel("../02 - Data for analysis/Flatiron/Population 2/agd_pop2_flatiron.xlsx")
Flatiron_OS_pop2<-read_excel("../02 - Data for analysis/Flatiron/Population
2/ipd_OS_pop2_flatiron.xlsx")
Flatiron_PFS_pop2<-read_excel("../02 - Data for analysis/Flatiron/Population
2/ipd_PFS_pop2_flatiron.xlsx")

# Population 3 - ESR1-mut, PIK3CA-mut and ≥12 months of prior ET + CDK4/6i population
dataIPD_pop3<-read_excel("../02 - Data for analysis/EMERALD/Population
3/original_ipd_pop3_elacestrant.xlsx")
dataAGD_pop3<-read_excel("../02 - Data for analysis/Flatiron/Population
3/agd_pop3_flatiron_ecog.xlsx")
Flatiron_OS_pop3<-read_excel("../02 - Data for analysis/Flatiron/Population
3/ipd_OS_pop3_flatiron.xlsx")
Flatiron_PFS_pop3<-read_excel("../02 - Data for analysis/Flatiron/Population
3/ipd_PFS_pop3_flatiron.xlsx")

# Data management of all tables
data_elacestrant_pop2<-dataIPD_pop2 %>%
select("USUBJID","ARM","ECOG","AGE","PRICHEFL","PRFULVFL","LINEENDO_1","LINEENDO_2",
"DIAG","AVAL_OS","AVAL_PFS","CNSR_PFS","CNSR_OS")%>%
  mutate(Population="Pop2")
data_elacestrant_pop3<-dataIPD_pop3 %>%
select("USUBJID","ARM","ECOG","AGE","PRICHEFL","PRFULVFL","LINEENDO_1","LINEENDO_2",
"DIAG","AVAL_OS","AVAL_PFS","CNSR_PFS","CNSR_OS")%>%
  mutate(Population="Pop3")
```

```
nrow(data_elacestrant_pop2) #78 patients
nrow(data_elacestrant_pop3) #27 patients


# Function to run MAIC ----------
MAIC_function<-
function(data_input,data_IPD,data_flatiron_OS,data_flatiron_PFS,weighted=TRUE,population=NULL){
  if(weighted==T){
    ## Step 1: Matching -----------------------------------
    objfn <- function(a1, X){ sum(exp(X %*% a1)) }
    gradfn <- function(a1, X){ colSums(sweep(X, 1, exp(X %*% a1), "*")) }

    # Center the data
    if(unique(data_IPD$Population)=="Pop2"){
       X.EM.0 <- sweep(with(data_IPD, cbind(AGE,AGE^2,PRICHEFL,LINEENDO_1,LINEENDO_2)), 2,
                    with(data_input, c(age.mean, age.mean^2 + age.sd^2,prior.ct.prop,et.l1.prop,et.l2.prop)), '-')

       print(opt1 <- optim(par = c(0,0,0,0,0), fn = objfn, gr = gradfn, X = X.EM.0, method = "BFGS"))
    }else{
      X.EM.0 <- sweep(with(data_IPD, cbind(AGE,AGE^2,LINEENDO_1,LINEENDO_2)), 2,
                   with(data_input, c(age.mean, age.mean^2 + age.sd^2,et.l1.prop,et.l2.prop)), '-')

      print(opt1 <- optim(par = c(0,0,0,0), fn = objfn, gr = gradfn, X = X.EM.0, method = "BFGS"))
    }

    a1 <- opt1$par
    # weights
    wt <- exp(X.EM.0 %*% a1)
    N_data <- nrow(X.EM.0)
    # rescaled weights
    wt_scaled <- (wt/ sum(wt)) * N_data

    summary_scaled_wt<-summary(wt_scaled)
    summary_wt<-summary(wt)

    # Effective sample size computation
    ESS<-sum(wt)^2/sum(wt^2)
    sum_wt_2<-sum(wt)^2
    sum_wt2<-sum(wt^2)
    wt<-as.vector(wt)

    #Convert variable diag in months
    data_IPD<- data_IPD %>% mutate(DIAG.2=DIAG*12)

    # Treatment effect modifiers distribution after re-weighting
    if(unique(data_IPD$Population)=="Pop2"){
      sum_wt_data<-data_IPD %>%
        mutate(wt) %>%
        summarise(AGE.mean= weighted.mean(AGE, wt),
                  AGE.SD = sqrt(sum(wt / sum(wt) * (AGE - AGE.mean)^2)),
                  PRICHEFL.prop= weighted.mean(PRICHEFL, wt),
                  PRFULVFL.prop=weighted.mean(PRFULVFL,wt),
                  LINEENDO_1.prop=weighted.mean(LINEENDO_1, wt),
                  LINEENDO_2.prop=weighted.mean(LINEENDO_2, wt),
                  ECOG.prop=weighted.mean(ECOG, wt),
                  DIAG.mean=weighted.mean(DIAG.2, wt),
                  DIAG.SD = sqrt(sum(wt / sum(wt) * (DIAG.2 - DIAG.mean)^2)))
    }else{
      sum_wt_data<-data_IPD %>%
        mutate(wt) %>%
        summarise(AGE.mean= weighted.mean(AGE, wt),
                  AGE.SD = sqrt(sum(wt / sum(wt) * (AGE - AGE.mean)^2)),
                  PRFULVFL.prop=weighted.mean(PRFULVFL,wt),
                  PRICHEFL.prop= weighted.mean(PRICHEFL, wt),
                  LINEENDO_1.prop=weighted.mean(LINEENDO_1, wt),
                  LINEENDO_2.prop=weighted.mean(LINEENDO_2, wt),
```

```
            ECOG.prop=weighted.mean(ECOG, wt),
            DIAG.mean=weighted.mean(DIAG.2, wt),
            DIAG.SD = sqrt(sum(wt / sum(wt) * (DIAG.2 - DIAG.mean)^2)))
  }
}

## Step 2: Unanchored MAIC running ----------------------------------

# Note regarding censoring:
#_In Surv function, censor corresponds to 0 for right censored, 1 for event
#_In ADAM spec censoring corresponds to 1 for censored and 0 for event
#_In Digit tool censoring corresponds to 1 for event and 0 for censored
# So need to convert both ADAM spec to surv input using 1-censor for the analysis

### Unweighted analysis ----------------------------------

## Gather dataset from whole population of EMERALD and Flatiron
if(weighted==T){
  data_IPD<-cbind(data_IPD,wt) %>%
    select("ARM","wt","AVAL_OS","AVAL_PFS","CNSR_PFS","CNSR_OS")
}else{
  data_IPD<-data_IPD %>%
    mutate(wt=1) # change the weights to 1 for unweighted analysis
}

## Prepare data sets for OS and PFS
data_flatiron_OS<-data_flatiron_OS %>%
  mutate(wt=1) %>%
  select("Treatment_label","wt","Time","Event") %>%
  rename(ARM=Treatment_label,AVAL_OS=Time,CNSR_OS=Event)

data_flatiron_PFS<-data_flatiron_PFS %>%
  mutate(wt=1) %>%
  select("Treatment_label","wt","Time","Event") %>%
  rename(ARM=Treatment_label,AVAL_PFS=Time,CNSR_PFS=Event)


## Gather all data into single one for OS and one for PFS
all_data_OS<- rbind(data_IPD %>%
                select(c("ARM","wt","AVAL_OS","CNSR_OS")) %>%
                mutate(CNSR_OS=1-CNSR_OS),data_flatiron_OS) # change the order for event/censor in both trial
to match the surv function requirements

all_data_PFS<- rbind(data_IPD %>%
                 select(c("ARM","wt","AVAL_PFS","CNSR_PFS")) %>%
                 mutate(CNSR_PFS=1-CNSR_PFS),data_flatiron_PFS) # change the order for event/censor in both
trial to match the surv function requirements

#### OS MAIC analysis ------------
all_data_OS$ARM <- as.factor(all_data_OS$ARM)
unique_arm<-levels(all_data_OS$ARM)
ref_arm<-unique_arm[unique_arm!="ELACESTRANT"]
KM_OS <- survfit2(Surv(AVAL_OS, CNSR_OS) ~ relevel(ARM, ref = ref_arm), data = all_data_OS,weights=wt)
options(digits=8)
survfit2(Surv(AVAL_OS, CNSR_OS) ~ relevel(ARM, ref = ref_arm), data = all_data_OS,weights=wt)
max_months <- max(all_data_OS$AVAL_OS)


# Generate curves for OS
KM_OS2<-KM_OS %>%
  ggsurvfit() +
  labs(
    x = "Months",
    y = "Probability of survival"
  ) + ggtitle("Overall survival stratified by ARM")+
  mytheme+
  add_confidence_interval() + scale_x_continuous(breaks = seq(0, max_months, by = 5)) +
```

```
    add_risktable(
      size=5,
      risktable_stats = c("{format(round(n.risk, 2), nsmall = 2)}",
                          "{format(round(n.event, 2), nsmall = 2)}"),
      stats_label = c("N effective patients at risk",
                      "N effective events")
    )
  #Fitting cox model to generate HR and 95% CI
  model_OS<-coxph(Surv(AVAL_OS, CNSR_OS) ~ relevel(ARM, ref = ref_arm),weights = wt, data =
all_data_OS)
  summary_model_OS<-summary(model_OS)

  #### PFS analysis ------------
  all_data_PFS$ARM <- as.factor(all_data_PFS$ARM)
  KM_PFS<- survfit2(Surv(AVAL_PFS, CNSR_PFS) ~ relevel(ARM, ref = ref_arm), data =
all_data_PFS,weights=wt)
  options(digits=8)
  survfit2(Surv(AVAL_PFS, CNSR_PFS) ~ relevel(ARM, ref = ref_arm), data = all_data_PFS,weights=wt)
  max_months <- max(all_data_PFS$AVAL_PFS)

  # Generate curves for PFS
  KM_PFS2<-KM_PFS %>%
    ggsurvfit() +
    labs(
      x = "Months",
      y = "Probability of survival"
    ) + ggtitle("Overall survival stratified by ARM")+
    mytheme+
    add_confidence_interval()+ scale_x_continuous(breaks = seq(0, max_months, by = 5)) +
    add_risktable(
      size=5,
      risktable_stats = c("{format(round(n.risk, 2), nsmall = 2)}",
                          "{format(round(n.event, 2), nsmall = 2)}"),
      stats_label = c("N effective patients at risk",
                      "N effective events")
    )

  #Fitting cox model to generate HR and 95% CI
  model_PFS<-coxph(Surv(AVAL_PFS, CNSR_PFS) ~ relevel(ARM, ref = ref_arm),weights = wt, data =
all_data_PFS)
  summary_model_PFS<-summary(model_PFS)

  # Return
  return(list(
    wt = if (weighted) wt else "no weighting",
    ESS = if (weighted) ESS else "no weighting",
    sum_wt_2=if (weighted) sum_wt_2 else NA,
    sum_wt2=if (weighted) sum_wt2 else NA,
    summary_wt = if (weighted) summary_wt else "no weighting",
    summary_scaled_wt = if (weighted) summary_scaled_wt else "no weighting",
    sum_wt_data = if (weighted) sum_wt_data else "no weighting",
    plot_wt = if (weighted) plot_wt else "no weighting",
    summary_model_OS = summary_model_OS,
    KM_OS2 = KM_OS2,
    model_OS = model_OS,
    summary_model_PFS = summary_model_PFS,
    KM_PFS2 = KM_PFS2,
    model_PFS = model_PFS,
    data_OS = all_data_OS,
    data_PFS = all_data_PFS
  ))
}
```

 # MAIC running ----------

```
# MAIC for pop 2
## Weighted analyses
MAICs_pop2_wt<-
MAIC_function(data_IPD=data_elacestrant_pop2,data_input=dataAGD_pop2,data_flatiron_OS=Flatir
on_OS_pop2, data_flatiron_PFS=Flatiron_PFS_pop2,weighted=T,population="Population 2")

## Unweighted analyses
MAICs_pop2_unwt<-
MAIC_function(data_IPD=data_elacestrant_pop2,data_input=dataAGD_pop2,data_flatiron_OS=Flatir
on_OS_pop2, data_flatiron_PFS=Flatiron_PFS_pop2,weighted=F,population="Population 2")


MAICs_pop2_wt$ESS
MAICs_pop2_wt$summary_model_OS
MAICs_pop2_wt$KM_OS2
MAICs_pop2_wt$summary_model_PFS
MAICs_pop2_wt$KM_PFS2

MAICs_pop2_unwt$summary_model_OS
MAICs_pop2_unwt$KM_OS2
MAICs_pop2_unwt$summary_model_PFS
MAICs_pop2_unwt$KM_PFS2


#MAIC for pop 3
## Weighted analyses
MAICs_pop3_wt<-
MAIC_function(data_IPD=data_elacestrant_pop3,data_input=dataAGD_pop3,data_flatiron_OS=Flatir
on_OS_pop3, data_flatiron_PFS=Flatiron_PFS_pop3,weighted=TRUE,population="Population 3")

## Unweighted analyses
MAICs_pop3_unwt<-
MAIC_function(data_IPD=data_elacestrant_pop3,data_input=dataAGD_pop3,data_flatiron_OS=Flatir
on_OS_pop3, data_flatiron_PFS=Flatiron_PFS_pop3,weighted=FALSE,population="Population 3")


MAICs_pop3_wt$ESS
MAICs_pop3_wt$summary_model_OS
MAICs_pop3_wt$KM_OS2
MAICs_pop3_wt$summary_model_PFS
MAICs_pop3_wt$KM_PFS2

MAICs_pop3_unwt$summary_model_OS
MAICs_pop3_unwt$KM_OS2
MAICs_pop3_unwt$summary_model_PFS
MAICs_pop3_unwt$KM_PFS2
```

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Breast Cancer Now
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Breast Cancer Now is the UK charity that's steered by world-class research and powered by life-changing care. We provide support for today and hope for the future.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Breast Cancer Now has received funding from a number of drug companies towards our support services. However, we do not receive any pharmaceutical funding for our Policy, Evidence and Influencing work, which includes our work on access to drugs. Over the last 12 months (April 2023-April 2024) we have received funding from the following companies listed in the stakeholder list for this appraisal: • AstraZeneca: £42,314.55 to support our helpline and Ask our Nurses service in May 2023, • Novartis: £109,985 to support our Service Pledge in August 2023, £46,000 to support our living with secondary breast cancer face-to-face service in June 2023 Breast Cancer Now hosts the UK Interdisciplinary Breast Cancer Symposium (UKIBCS) alongside a number of partners including professional bodies and charities. The meeting is held every 2 years and the UKIBCS provides a space to bring together those with an interest in breast cancer research and treatment to advance understanding of the disease. The event is managed by a third party who receive and process sponsorship on behalf of the host and partners. Sponsors have no control over the running of the event and editorial control has been retained by the UKIBCS executive board.

	In the past 12 months (since April 2023), this has included the following listed on this appraisal matrix: • Menarini Stemline: £15,500 for a Gold supporters package at UKIBCS (June 2023) • AstraZeneca: £30,000 for a platinum supporters package at UKIBCS (April 2023) and £3k for an additional stand at UKIBCS (December 2023) • Eisai: £3k for an exhibitor package at UKBICS (May 2023) • Novartis: £30k for a platinum supporters package at UKIBCS (May 2023) and £50k for advertising space at UKIBCS (December 2023). • Pfizer: £6k for an exhibitors package at UKBICS (November 2023) • Pierre Fabre: £3k for an exhibitors package at UKBICS (October 2023).
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	At Breast Cancer Now we use our various networks of people affected by breast cancer to gather information about patient experience. This includes our online Breast Cancer Now Forum and our online and face to face services. We have also spoken to a patient with secondary breast cancer who has received elacestrant as part of their treatment to inform this response.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Secondary breast cancer, sometimes known as advanced or metastatic breast cancer, occurs when cancer originating in the breast spreads to other parts of the body, most commonly the lungs, brain, bones or liver. There is no cure for secondary breast cancer, so treatment aims to control and slow the spread of the cancer, relieve symptoms and give people the best quality of life for as long as possible. Someone can be diagnosed with secondary breast cancer from the start, or they can be diagnosed with the condition subsequent to a primary breast cancer diagnosis. Oestrogen receptor (ER)-positive, HER2-negative is the most common sub-type of breast cancer, accounting for 80% of cases. These cancers are typically treated with a combination of endocrine therapies (including aromatase inhibitors) and targeted therapies. If patients experience progression following several lines of endocrine therapy and targeted therapies they will generally be treated with chemotherapy. Sustained treatment with endocrine therapies may result in endocrine resistance, including resistance due to Oestrogen-receptor 1 (ESR1) acquired mutations. ESR1 mutations are rare in primary breast cancer, but become more frequent in secondary breast cancers, typically developing after previous exposure to aromatase inhibitors. ESR1 mutations are not typically tested for in the NHS in England (the tests do not appear on the National Genomic Test Directory), so it is not known how many secondary breast cancer patients have these mutations. Secondary breast cancer symptoms can have a major impact on people's quality of life. They will vary depending on where the cancer has spread to, but general symptoms can include feeling constantly tired, nausea, weight loss and loss of appetite. Bone pain and bone fractures can occur if cancer has spread to the bones. Symptoms such as breathlessness and pain while breathing can occur if cancer has spread to the lungs. Breast cancer treatments themselves can also cause side effects, which is a significant source of concern for patients. These side effects can have a major impact on people's day-to-day lives, quality of life, health and wellbeing. Different patients will react differently to drugs, so side-effects are not easy to predict. Diagnosis with secondary breast cancer can have a significant emotional toll and practical implications for those diagnosed and their families and friends. After their diagnosis, patients may feel overwhelmed, anxious, depressed and isolated. Beyond the emotional toll of the diagnosis, the practicalities of managing their condition (which often involves travelling to regular hospital appointments) alongside day-to-day activities like work, household and parental responsibilities can be difficult to manage.

	Many patients at this stage of their treatment for secondary breast cancer have a significant desire to find treatments that will halt progression and extend life for as long as possible. They also have a strong desire to retain quality of life and spend time with their loved ones.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Patients diagnosed with ER positive, HER2 negative secondary breast cancer, will typically be treated with an aromatase inhibitor (such as anastrazole, exemestane or letrozole) and a CDK 4/6 inhibitor (such as abemaciclib, ribociclib or palbociclib). If they experience progression on this combination of drugs, they may be offered everolimus and exemestane, or fulvestrant and alpelisib (if they show a PIK3CA mutation). If they experience progression after several lines of endocrine therapy and targeted therapies, they will typically be given chemotherapy. Patients are keen for more and better options to be available to treat secondary breast cancer. A patient we spoke to currently receiving elacestrant via private medical insurance said “there are… frankly no other options for me (and others), and so this is our last chance to delay the inevitable a little longer”.
8. Is there an unmet need for patients with this condition?	Yes – These patients have experienced progression after at least one endocrine treatment, and have an ESR1 mutation. They currently have limited options for further treatment, and no specific targeted treatment options.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The EMERALD trial (Bidard et. al. 2022) was a randomised, open-label, phase III trial that compared patients treated with elacestrant 400mg orally once daily (n=239), to those treated with endocrine monotherapy (n=238). All patients had ER-positive, HER2-negative secondary breast cancer, and had received one to two lines of endocrine therapy and a CDK 4/6 inhibitor. 47.8% of patients had a detected ESR1 mutation. Median progression free survival (PFS) was 3.8months (compared to 1.9months for comparator) in the ESR1 cohort. The researchers found a 45% relative reduction in progression or death in the ESR1 cohort. We are not aware of any currently published data on absolute risk reduction, or overall survival. Patients at this stage in their treatment for secondary breast cancer face limited options for further treatment. Elacestrant offers an additional option, beyond chemotherapy, that may offer benefits for these patients. The treatment can be taken orally, which is appealing for many patients, as it does not require regular hospital visits. One patient we spoke to, who is currently receiving elacestrant through private medical insurance, said “my side-effects are non-existent, and as a pill it is easy to take and does not require hospital visits”.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Secondary breast cancer patients are often concerned about potential side-effects when starting a new medication, and the potential for these to impact on their quality of life. Side effects were reported by 92% of patients receiving elacestrant as part of the EMERALD clinical trial. The most common side-effects were nausea, fatigue, vomiting, decreased appetite and arthralgia. These side-effects can impact on patients lives if they cannot be appropriately managed. Every treatment for breast cancer has some side effects and each patient's situation will be different with side effects impacting some patients more than others. Patients' willingness to receive treatments will vary, however, as long as all the side effects are clearly discussed with the patient, they will be able to make their own choice as to the level of risk they will be willing to take balanced against the potential benefit of that treatment option.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Not that we are aware.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None that we are aware of.

Other issues

13. Are there any other issues that you would like the committee to consider?	The committee will need to consider the need for genetic testing for this treatment. As many ESR1 mutations are acquired, additional testing would be required to establish the presence of these mutations and identify eligible patients for treatment with elacestrant.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Patients with ER-positive, HER2 negative secondary breast cancer who have experienced progression after endocrine treatments face limited options for further treatment. This can have a devastating impact on the patient and their family and friends. • Endocrine resistance, including resistance due to ESR1 mutations may develop after sustained treatment with endocrine therapies. Those with ESR1 mutations do not currently have access to targeted treatments. • The EMERALD trial found that patients with an ESR1 mutation treated with elacestrant experienced median progression free survival of 3.8months (compared to 1.9months for comparator). There was a 45% relative reduction in progression or death in the ESR1 cohort. • Secondary breast cancer patients are keen for more and better treatment options to become available and Elacestrant would provide an additional targeted treatment option for those with ESR1 mutations. Another particular benefit of this treatment to the patient is that it is administered orally and does not require additional hospital visits. • Patients are likely to experience side-effects, including nausea, fatigue, vomiting, decreased appetite and arthralgia. These side-effects would need to be appropriately managed. As long as side effects are clearly discussed with the patient, they will be able to make their own choice as to the level of risk they will be willing to take balanced against the potential benefit of that treatment option.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Your response should not be longer than 10 pages

About you

1.Your name	[redacted]
2. Name of organisation	Make 2nds Count (Registered Charity Number: SC048268), Gyleworks, 34 South Gyle Crescent, Edinburgh, EH12 9EB
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Make 2nds Count is a UK-wide patient and family focussed charity dedicated to giving hope to women and men living with secondary breast cancer. Our fundraising income mainly relies on individual fundraising efforts through marathons, skydiving, dance challenges and events, and grants provided by trusts and foundations. Our online patient support group has 1500 members. You can learn more about Make 2nds Count by visiting our website: https://make2ndscount.co.uk/
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	Yes, as follows: AstraZeneca - £25,000 - sponsorship of the Make 2nds Count Secondary Breast Cancer Patient Summit, a patient education event being held on 9-11th July 2024 in Liverpool. Pfizer - £25,000 - educational grant to support the Make 2nds Count Secondary Breast Cancer Patient Summit, a patient education event being held on 9-11th July 2024 in Liverpool. The Secondary Breast Cancer Patient Summit, organised by Make 2nds Count, will be the first national patient-focused conference in the UK for secondary breast cancer. You can read more about this conference here.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	A Google Survey was provided to our community group on social media during mid-March to mid-April 2024. This survey included the questions noted in this form. Eighteen patients completed the survey. Each response was read and themes extracted. The data from this survey has been used to populate the answers in this form.

Living with the condition

6. What is it like to live with the condition? **What do carers experience when caring for someone with the condition?**	The main theme from surveyed patients was the large amount of uncertainty they have to live with because of secondary breast cancer. The uncertainty was described as originating from having to live with a disease that patients know is incurable. Thereby, patients know that their current treatment will eventually stop working and their health will deteriorate, but not knowing when this will happen causes extensive uncertainty and distress regarding their futures. Many respondents described having to live "scan to scan" and the impact of the lack of knowing what their future health outcome will be. For example, one patient stated their diagnosis was "like being on a roller coaster, with lots of ups and downs, but at some point we will run out of track... and we don't know when that will be... we just hope we can ride for as long as possible." Additionally, many patients described how physically and mentally difficult it can be to live with this disease. One respondent simply described that living with this condition was "Hell". Patients all described how living with this disease impacts their loved ones. Particularly, those with young children described how they have to live in "constant fear" that they will not live long enough to see them into adulthood. One patient stated: "Every big occasion or anything to do with my children you just fear for their future." Patients described how their loved ones felt sad, hopeless, helpless and had to live in a constant state of fear because of the uncertainty of the future health outcome of the patient. Many mentioned that loved ones had to reduce their working hours to help the patient with day to day activities and the financial pressures their families experience.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Many patients described the limited number of treatment options available to them, particularly after a first line of treatment had failed. Patients described how side effects of treatment caused a diminished quality of life and resulted in them having to stop working, go to the hospital more and reduce the amount of energy they have to do things they enjoy. Patients also described a "postcode lottery" of treatment availability across the UK with one patient putting this bluntly: "Some drugs are available in Scotland but not in England. Since when is health dictated by postcode." Given that patients know their treatment lines will fail and that limited further options exist, then being denied an option because of locality was highly distressing. For example, one patient wrote "It hurts to know there are treatments being used elsewhere but because I am in the UK and NHS I don't have access to them all, how is that fair?" Another patient wrote "At times I have found it unfair as I have not been able to access treatments that could have worked for me and that could have been less harsh than chemotherapy." A different patient also said "I feel scared knowing that one day my treatment options will run out, and all I can do is hope that by the time I need them, more options will be available." Patients similarly described that a "postcode lottery" influenced the level of NHS care across the UK. Many patients described how their local hospital might not have nurses that specialise in secondary breast cancer resulting in feelings of isolation. One patient noted they drove "2-hours one way to receive treatment out of my local area as it's far superior to what I could receive where I live."

8. Is there an unmet need for patients with this condition?	Yes. Endocrine therapy plus CDK4/6 inhibition is a commonly used standard-of-care (SOC) first-line therapy in ER+ metastatic breast cancer [1]. However, most of these patients will develop therapeutic resistance, many by acquiring an activating mutation in the gene *ESR1*, which codes for the ER [2]. The use of sequential endocrine monotherapy is the current SOC for patients after progression on CDK4/6 inhibitor plus endocrine therapy [1]. Following further resistance to this endocrine monotherapy, patients will likely then have to undergo chemotherapy. The EMERALD III trial [3] has shown that Elacestrant is an effective and potent endocrine blocker and can overcome endocrine resistance in patients with *ESR1* mutations. Elacestrant was more effective than other endocrine monotherapy (including fulvestrant) especially in patients with *ESR1*-mutant tumours. Patients described knowing that if diagnosed with ER+ secondary breast cancer that their hormonal therapy will eventually stop working. Many described that once this happens they know they face a limited number of options and in general have a poor prognosis. Many patients described wanting to have alternatives to chemotherapy if they start to develop resistance to their current endocrine therapy. For example, one patient, who knew that the treatment next available to them was chemotherapy based, stated “The opportunity to have less harsh treatments that extend life are definitely something me and my family are interested in.” The majority of patients described the additional hope given to them by new treatments that have been shown to extend time until further disease progression and extended overall survival time. For example, one patient wrote “We need more positive alternative options for continuing treatments so that as our disease progresses we have hope and some kind of future to be able to stay with our loved ones much longer.” References: [1] National Comprehensive Cancer Network: *Breast Cancer (version 2.2022)*. Plymouth Meeting, PA, National Comprehensive Cancer Network, 2022. [2] Jeselsohn R, Buchwalter G, De Angelis C, *et al*: ESR1 mutations—A mechanism for acquired endocrine resistance in breast cancer. *Nat Rev Clin Oncol* 12:573-583, 2015 [3] Bidard F-C, Kaklamani VG, Neven P, *et al*: Elacestrant (oral selective estrogen receptor degrader) versus

	standard endocrine therapy for estrogen receptor–positive, human epidermal growth factor receptor 2–negative advanced breast cancer: Results from the randomized phase III EMERALD trial. *J Clin Oncol* 40:3246-3256, 2022

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The principal advantage patients noted was knowing that this treatment line has been shown to extend time until further disease progression and overall survival. This additional time with loved ones was stated of critical importance. Patients wrote that advantages included “More chance of surviving longer”, “Another option for those whose treatment has stopped working, and to extend our lives”, “It gives people more time with their families” and “longevity”. Patients also noted the advantage of only having to take a tablet, compared to intramuscular injections with fulvestrant. For patients this would result in fewer hospital visits and this was stated as a clear logistical advantage. Patients also described the advantages of having to delay chemotherapy and all of the negative side effects associated with this, which they knew have comparatively harsher side effects than treatment with Elacestrant.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The vast majority of patients stated that they did not see any disadvantages to this treatment line. Side effects were mentioned by some, but it was additionally noted that Elacestrant side effects were comparable to what they are already experiencing with hormonal therapy and viewed as less harsh than chemotherapy side effects. Two patients did note that if this treatment line was expensive it would have an impact on NHS budgets.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The EMERALD III clinical trial showed that in the second-line metastatic setting Elacestrant was more effective than other endocrine monotherapy (including fulvestrant), especially in patients with *ESR1*-mutant tumours [1]. Given that 40% of patients develop *ESR1* mutations after disease progression on endocrine therapy [2] there will be *ESR1* negative patients who wouldn't likely benefit as much as *ESR1* positive patients from Elacestrant. This disparity in potential benefit based on *ESR1* mutation status was noted by patients. Patients also noted that elderly patients who are less likely to be able to tolerate the side effects of chemotherapy would likely benefit more from this approval, than more physically fit patients who may experience comparatively less harsh side effects if their next treatment line was chemotherapy. Similarly, patients noted how younger patients, who are more likely to have to continue to work and/or might have young children to care for, will also likely have a higher benefit as chemotherapy treatment is more likely to impact a patient's ability to work and care for children's day to day needs. It was also raised that patients with lobular breast cancer may benefit more, as lobular breast cancer is known not to respond to chemotherapy as well as ductal. References: [1] Bidard F-C, Kaklamani VG, Neven P, *et al*: Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor–positive, human epidermal growth factor receptor 2–negative advanced breast cancer: Results from the randomized phase III EMERALD trial. *J Clin Oncol* 40:3246-3256, 2022 [2] Herzog SK, Fuqua SA: ESR1 mutations and therapeutic resistance in metastatic breast cancer: Progress and remaining challenges. *Br J Cancer* 126:174-186, 2022

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We are not aware of any potential equality issues.

Other issues

13. Are there any other issues that you would like the committee to consider?	Patients mentioned how they would like to see the speed of which new medicines achieve NHS approval accelerated. One patient wrote “Please don’t delay. While you decide we die.” Many patients also emphasised that decisions regarding new efficacious treatment lines not only impact the patient but many other individuals: “Consider the huge effect this has not only on the individuals but on their partners, their children, their parents, their siblings, the rest of their families and their friends. The ripples are massive.” Another patient also wrote how the benefits are more than just physical and wanted the committee to consider “The boost to mental health that having additional lines of treatment can bring.” The patients discussed cost effectiveness. Key points raised are that an improved side effect profile and decrease in complications reduces hospital admissions and additional care required, as well as the wider economic impact of longevity and wellbeing which allows patients with this condition to be able to contribute to society.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	● Secondary breast cancer patients live with a large amount of uncertainty regarding their future health outcomes which causes extreme distress, both for the patient and for loved ones. The approval of new treatment lines that are known to extend time until further disease progression provides hope and can alleviate some of this distress. ● In general, secondary breast cancer patients feel they have limited treatment options available to them when treatment lines start to fail and their main priority is an extension of time with loved ones. This could be summarised in the patient quote: "Living with secondary breast cancer is a life sentence. Our needs are very simple. To be able to spend as long as possible with our loved ones and for those fortunate enough to have children to see them grow up. No effective drugs should be denied." ● Patients note the benefit of Elacestrant being a tablet, compared to intramuscular injections with Fulvestrant enabling fewer hospital visits for the patient. They described how this targeted treatment has comparatively less harsh side effects than chemotherapy and because Elacestrant delays disease progression, it can delay the time until chemotherapy treatment. ● The vast majority of patients did not note any disadvantages to the approval to Elacestrant, except for potential NHS cost (which they believed would be justified) and the risk of side effects (but they felt these were much milder than chemotherapy and similar to the existing SOC). ● When surveyed patients were asked how they felt about efficacious treatments being rejected for cost reasons they unanimously expressed a sentiment that this was unacceptable. If a treatment was already approved elsewhere around the world, but was not to be approved on the NHS in the UK because of cost reasons, this would exacerbate the health inequalities this patient group already experience.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	METUPUK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	METUPUK is a volunteer led patient advocacy organisation working for the unmet needs of patients with metastatic breast cancer (MBC). Our three main objectives are: raising MBC awareness and education; campaigning for equitable treatment, including access to drugs; and improvements in patient care. Our services aim to inform patients with primary breast cancer, their family and friends and clinicians of the red flag signs and symptoms of metastatic breast cancer. For patients with metastatic breast cancer, we campaign for improved access to drugs and treatments. This may include addressing disparities and inequalities in accessing treatment and clinical trials in the four nations of the UK, or between different commissioning groups within a given nation. We have created and maintain a clinical trials dashboard on our website showing a breakdown of current MBC trials in the UK by location and trial type. We also campaign for access to new therapeutics and radiotherapy treatments, so NHS and private patients have the same access to treatment. We call on Trusts to collect accurate and timely data on their patients with MBC. We are members of the Audit Advisory Committee for NAoMe, the national audit of metastatic breast cancer. Through our social media channels, we provide signposting for peer support and to other charitable organizations that also offer support. We became a registered charity in 2021, but the organisation began as a small group of patients frustrated by the poor prognosis for MBC in 2016 and has grown since then. We are not a

	membership organisation, but we do reach out to the metastatic patient community with over 9000 followers on social media platforms. Our funding is mainly from public donations, and our accounts are published on the Charity Commission website. All our trustees and volunteers are unpaid.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	No
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We used our social media channels of Facebook, Instagram and Twitter to gather experiences of patients on elacestrant. We also reached out to patients with oestrogen receptor-positive HER2-negative MBC who could benefit from this treatment but had not been on a trial. We wanted to know what a new oral endocrine treatment targeted to a mutation in their cancer would mean to patients.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with MBC is to live with uncertainty. We live from scan to scan, and even if our treatment appears to be working well, we never know if our cancer is progressing. It is incredibly difficult to plan anything beyond three or six months in the future. Even with the best available drug therapy, for most patients, decades of life will be lost. It is a severe life-limiting disease. We mourn this loss of life - milestones, precious memories with families and friends, ambitions for future careers, income and contributions to our communities and society. Some of us grieve the loss of being parents and others agonise over leaving children parentless. A METUPUK patient advocate describes living with MBC: Living with MBC brings a level of sadness which is always there and cannot be shifted. You are constantly aware that your life is time limited and planning of any kind is exceptionally difficult. You feel helpless and despair that you have no control over your illness and are wholly dependent on the availability of drugs to keep you alive. The psychological benefits of knowing that medical advancements continue to be pursued and will be made available cannot be emphasised enough- it reduces the mental stress of MBC and brings real hope. MBC is also incredibly difficult for carers. Partners find their role in the family changes quite suddenly from lover to carer for the patient, often balancing this with the financial need to work and sometimes manage childcare. Many patients have children under 18 living with them who face the considerable difficulties of being a young carer while balancing their studies and losing out on their youth. Patients' parents face the awful prospect of their children dying before them, with very little support. A supporter whose wife has metastatic breast cancer describes how "our lives are turned upside-down, organised around treatments and care. We make plans we hope will come to pass but do not presume. We value the life of those we love like we have never done before, and knowing it will not last, we cherish what we have" A young newly married man explained, "There are so many compromises to be made that you don't even think about. I love my wife and spending time with her, so it's largely positive although being on call when she's sick is challenging. The mental side is very hard. I don't like seeing her so sick. It makes me sad." His wife has died since this statement was written. She was 32.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Patients with oestrogen receptor-positive HER2-negative metastatic breast cancer value targeted treatments over untargeted chemotherapy. They are excited by precision treatments which target mutations in their cancer. Patients generally prefer treatments which are taken as a tablet at home, as opposed to injections and infusions which must be administered in hospital settings. Patients feel frustrated when new more effective treatments with reduced side effects take a long time to reach routine NHS care. A patient writes: "A new pill treatment would be wonderful, giving me the chance to live a fuller, more normal life, as well as the hope of more time with my family and friends should it work well for me." Another patient comments: "What is the point of these drugs being developed if patients cannot get access and benefit from them?" Most patients with oestrogen receptor-positive HER2-negative metastatic breast cancer will get two lines of endocrine treatment on the NHS. Many patients would prefer more lines of endocrine treatment, particularly treatments which can circumvent endocrine resistance in their cancer. Elacestrant offers the promise of an additional line of endocrine treatment in patients with an ESR1 mutation. Chemotherapy also means that patient's lives revolve around hospital visits for treatment. One patient who had previously been on endocrine treatment writes: "I am now on IV chemotherapy, which is much harder on my body with several harsh side effects. It is also difficult to lead a normal life when I have weekly treatments, as it is impossible to plan ahead, especially for things like holidays, which are really important for making memories and enjoying life. At the moment, chemotherapy seems to be the only treatment that will be available to me for the foreseeable future."
8. Is there an unmet need for patients with this condition?	Yes there is an unmet need for elacestrant. After progression on first and second line endocrine treatment, there are limited options for patients with oestrogen receptor-positive HER2-negative metastatic breast cancer. Elacestrant has been shown to be particularly useful for patients with ESR1 mutations who have progressed on endocrine treatments. ESR1 mutations can develop over time and are associated with resistance to endocrine treatments.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Feedback on from patients about the appraisal of a new endocrine treatment has been very positive. "I really hope this is approved by NICE; it will give us another option after our first line and so longer without having IV chemo." The patients we consulted with were conscious that every line of treatment is vital for them to extend their lives. "It would be great to know there was another possible hormone treatment in the pipeline. I'm nearly 5 years in (after de novo diagnosis). I started on letrozole + palbociclib and have been on fulvestrant for the last 18 months but fear it's getting to the end of its efficacy. Obviously, without being tested it's impossible to know if we have the necessary gene but it's something to keep us having a closer to normal life, and give us hope." "This would be amazing, to have another treatment option for stage 4 breast cancer, every single treatment option means so much to me as a stage 4 patient. They all mean time with my son seeing him grow up, reaching milestones that without these new and extra treatment lines wouldn't be possible." Genomic testing is an important part of this appraisal for patients. If patients test negative for an ESR1 mutation, it will be easier for them to accept that elacestrant is unlikely to be of benefit to them. If they test positive for an ESR1 mutation, then they can be reassured that they are receiving an evidence based treatment targeted to their particular cancer. There is some uncertainty among patients about how the genomic testing will be done. The protocol in the EMERALD Trial was to use Guardant 360 CDx, a ctDNA based blood biopsy. There are other treatments for metastatic breast cancer used in the NHS that require genomic testing from a tissue sample. For example alpelisib is targeted against a mutation in the PIK3CA gene, and is tested for using a tissue sample. Support for genomic testing in cancer among the patient community is summarised by this quote from our consultation: "I think testing each cancer is important as the drugs are very targeted and we should all be benefiting from this. Progressive cancer needs to be slowed down and stopped, too many people are suffering. Oncologists need to know more about each cancer and offer what is on offer!!!" Another patient comments, "This is true personalised care and what the aim should be in the NHS."

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	As with all drugs elacestrant has side effects. In the EMERALD trial (Bidard, FC *et al*, 2022) nausea, vomiting and decreased appetite occurred more frequently with elacestrant than in the control arm of endocrine treatment monotherapy. However, most side effects were mild or moderate, and patients and their oncologists are accustomed to managing gastrointestinal symptoms. Elacestrant has been shown in trials to increase progression free survival. For most patients increasing overall survival time is highly valued, and data for OS is immature. However, patients do also value increasing progression free survival, which can delay the need for chemotherapy. For many patients, increased PFS translates to reduced tumour load and better management of symptoms. Metastatic breast cancer is a severe disease with a very short life expectancy. Treatments which increase quality of life so remaining time can be spent in a way that reflects individual's preferences are very important. Bidard FC, Kaklamani VG, Neven P, *et al*. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. *J Clin Oncol.* 2022 May 18

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	No comments, patient selection is a clinical decision.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No issues noted

Other issues

13. Are there any other issues that you would like the committee to consider?	Patients would like clarity about how alterations in the ESR1 gene will be detected. Will a ctDNA test be used, as in the EMERALD trial, or will a tissue sample be used? If a tissue sample is used will a new sample be required or can an archived sample be used? If a ctDNA test is used, is it as sensitive as testing a tissue sample?

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Patients with oestrogen receptor-positive HER2-negative MBC value an additional line of endocrine treatment. Many worry that chemotherapy will not be effective and will reduce their quality of life. • Patients prefer oral treatments taken at home, because it is easier for them to plan ahead, fulfil their commitments, book holidays and make memories. • Patients support testing for ESR1 mutations and would like clarity about how this will be done. While ctDNA tests are much easier for patients, they would like reassurance about their sensitivity. • Elacestrant addresses an unmet need. There is no oral SERD available on the NHS and no treatments are targeted to alterations in ESR1 gene. • Elacestrant increases progression free survival giving patients a longer time with a reduced tumour load. For most patients this translates to improved management of symptoms and a better quality of life.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

NICE National Institute for Health and Care Excellence

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Thursday 15 August 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Professor Mark Beresford
2. Name of organisation	Dyson Cancer Centre, Bath and UK Breast Cancer Group
3. Job title or position	Consultant Oncologist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment? ☒ A specialist in the clinical evidence base for oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes

7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Primary aims are to prolong life and maintain quality of life. An important and relevant secondary aim is to defer or avoid the need for cytotoxic chemotherapy
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Improvement in symptoms (if symptomatic) and/or radiological reduction in tumour/metastases burden. For some patients stable disease is an acceptable outcome at this stage of the disease .
10. In your view, is there an unmet need for patients and healthcare professionals in oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment?	Yes. Limited and relatively toxic endocrine therapy options available before moving on to chemotherapy.
11. How is oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	ESMO guidelines recommend maximising endocrine therapy options before moving on to cytotoxic treatments. Current options are everolimus and exemestane (poorly tolerated), alpelisib plus fulvestrant (limited patient cohort requiring PI3K mutation, not very effective and poorly tolerated) or fulvestrant alone (currently not NHS-funded as single agent). The technology would give an effective and well-tolerated option for the subgroup of patients with ESR1 mutations who have responded well to cdki 4/6 therapy

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	This is a new option of treatment post cdki inhibitors. It would be used in the subgroup of patients with ESR1 mutations who have had at least 1 2months control with cdki therapy. Prescribed and monitored in secondary care. Investment needed to introduce the technology: patients will require ESR1 mutation testing. This is an acquired mutation with endocrine resistance so will require testing at the point of progression on cdki therapy. It could be either with a repeat tumour biopsy or, more practically, ctDNA testing. The test could either be an NGS panel (this would give information about other potential targets/mutations relevant to other drugs and might be more cost-effective and clinically useful in the long-term) or specific ESR1 droplet pCR for this technology.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes. There may be prolongation of life. Certainly would delay the need for chemotherapy and maintain quality of life for many patients. Also importantly help with capacity in chemotherapy units.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No (assuming the suggested criteria of ESR1 mutated after at least 12 months control on cdki)
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient	No – likely to be easier to administer and manage (less toxicity and dose modifications expected)

acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Yes – there will be quality of life benefits for patients (fewer side effects, better tolerated, psychological reassurance of another line of non-cytotoxic therapy). Also benefits to oncology services with an easily administered treatment requiring less intense monitoring. Potentially fewer outpatient oncology encounters and blood tests required, particularly once established on the new technology. We could review patients every 3 months in clinic with scan results rather than monthly appointments and blood tests for everolimus.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes, a step change in that for the first time (at least for a subgroup of patients) we have an effective non-chemotherapy option after cdki4/6 therapy.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Minimal and better than current options
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting?	The trial had single agent fulvestrant as an option in the comparator arm. Although it is known to be effective for some patients, we don't have access to this currently in the UK. For this reason a more appropriate comparator is considered as exemestane plus everolimus.

• What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA421 and TA816?	No
23. How do data on real-world experience compare with the trial data?	We have little real-world experience and no published data yet.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could	No equality issues

• exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	
25. Elacestrant is indicated for the treatment of people who have been through the menopause, and men, with oestrogen receptor-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least 1 line of endocrine therapy including a CDK 4/6 inhibitor. Where in the treatment pathway would you expect to use elacestrant?	As described but only in patients who have responded well to first line endocrine therapy (ie 12 months or more on cdki), suggesting hormonal sensitivity and acquired resistance.
26. When would you expect diagnostic testing for the ESR1 mutation to happen?	At point of progression on cdki therapy
27. What are the relevant comparators for elacestrant?	Exemestane and everolimus
28. Are clinical outcomes likely to be different depending on whether the locally advanced or	Unknown

metastatic breast cancer is oestrogen receptor-positive or progesterone receptor-positive?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Delays time to chemotherapy

Maintains quality of life for patients

Low toxicity

Favourable for oncology service capacity

Appropriate to target group most likely to benefit (ESR1 mutation and 12 months or more benefit from cdki)

Thank you for your time.

Your privacy

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Single Technology Appraisal

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment or caring for a patient with oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Thursday 15 August 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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Patient expert statement

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Part 1: Living with this condition or caring for a patient with oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment

Table 1 About you, oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment, current treatments and equality

1. Your name	Kirstin Spencer
2. Are you (please tick all that apply)	☒ A patient with oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	METUP UK (Metastatic Exchange To Unleash Power)
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations

Patient expert statement

	submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment? **If you are a carer (for someone with oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment) please share your experience of caring for them**	It is devastating that although ER+ breast cancer patients are told their cancer is 'treatable', research indicates, that for many patients there is a lack of effective treatment options from the second line setting and beyond (Brett *et al.* 2021; Ferraro *et al.* 2022). ER overexpression has also been found to confer resistance to oestrogen deprivation (Traphagen *et al.* 2021). For these patients – of which I am one myself - expecting several years of effective endocrine therapy but who progress quickly on their first line treatment in the metastatic breast cancer (MBC) setting, developing an ESR1 mutation and becoming insensitive to ER therapy, can be particularly challenging. It can invoke anxiety and a multitude of physical and mental issues accompanying the frustration of relentless disease progression.

	For our families, certainly for my daughter there is a constant worry, "When will mummy die? Why can she not get any medicine that works?". The guilt of being forced to abandon your vulnerable child is not a torturous, fleeting nightmare either but a daily reality to wake up to. Somehow, you all have to learn to live with the reality of being an innocent on death row. Will you get a reprieve? Find a new medication that works… and if you do, will you be able to access it on the NHS? Personally, it was disappointing to learn that this alleged treatable ER+ disease, after an initial short period of complete response to Letrozole (and questionably Palbociclib - as I never tolerated it well) progressed. Initially this was suggested as arthritis but a second opinion confirmed metastatic breast cancer. A later bone biopsy showed ESR1 – Y537S and PIK3CA – E545K. I then learned that mutations can be acquired making the cancer more aggressive from the medication you take to stop it. In this case and many others, it was likely Letrozole. References: Brett, J., Spring, L., Bardia A., Wander S., (2021) 'ESR1 mutation as an emerging clinical biomarker in metastatic hormone receptor-positive breast cancer', *Breast Cancer Res.* Aug 15;**23**(1):85. doi: 10.1186/s13058-021-01462-3. PMID: 34392831; PMCID: PMC8365900. Ferraro E., Walsh E., Tao E., Chandarlapaty S., Jhaveri K., (2022) 'Accelerating drug development in breast cancer: New frontiers for ER inhibition', *Cancer Treatment Reviews*, 109, p. 102432, doi:10.1016/j.ctrv.2022.102432.

	Traphagen, N.A., Hosford, S., Jiang, A., Marotti, J., Brauer, B., Demidenko, E., Miller, T., (2021) 'High estrogen receptor alpha activation confers resistance to estrogen deprivation and is required for therapeutic response to estrogen in breast cancer', *Oncogene*, **40**(19), pp. 3408–3421. doi:10.1038/s41388-021-01782-w.
7a. What do you think of the current treatments and care available for oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	7a. Current treatments simply do not address the issues known with ESR1 mutated oestrogen positive disease discovered in 1997 (Zhang *et al.*) and established as having a significant role in oestrogen resistance since sequencing of metastatic breast cancer in 2014 (Robinson *et al.* 2013; Toy *et al.* 2013; Jeselsohn *et al.* 2014). MBC patients dislike having buttock injections for fulvestrant. 7b. I am not sure how many patients are aware of the issues they face with an ESR1 mutation (not to mention that these can often arrive with co-mutations to support nullification of anti-oestrogen therapy). I have only had feedback of huge relief that finally there may be hope of extending oestrogen therapy for ESR1 mutated oestrogen receptor positive HER2-negative metastatic breast cancer Currently patients are not tested for an ESR1 mutation and have no choice but to accept the standard of care (SOC) offered. Collaboration with American Breast Cancer Charities where women are already being treated with Elacestrant (approved by FDA January 27, 2023) has supported and informed patient knowledge with real world experiences and outcomes. This has been further informed by the EMERALD trial data. References:

	Jeselsohn R, Yelensky, R., Buchwalter, G. *et al.* 'Emergence of constitutively active estrogen receptor-α mutations in pre-treated advanced estrogen receptor-positive breast cancer' *Clin Cancer Res Off J Am Assoc Cancer Res.* 2014;**20**:1757–1767. doi: 10.1158/1078-0432.CCR-13-2332. - DOI - PMC -PubMed Robinson, D., Wu, YM., Vats, P. *et al.* Activating *ESR1* mutations in hormone-resistant metastatic breast cancer. *Nat Genet* **45**, 1446–1451 (2013). https://doi.org/10.1038/ng.2823 Toy, W., Shen, Y., Won, H. *et al. ESR1* ligand-binding domain mutations in hormone-resistant breast cancer. *Nat Genet* **45**, 1439–1445 (2013). https://doi.org/10.1038/ng.2822 Zhang, Q., Borg, A., Wolf, D. Oesterreich, S. *et al.* 'An estrogen receptor mutant with strong hormone-independent activity from a metastatic breast cancer'. *Cancer Research* 1997 Apr 1;**57**(7):1244-9. PMID: 9102207.
8. If there are disadvantages for patients of current NHS treatments for oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Up to half of ER+ MBC patients show intrinsic resistance to endocrine therapy, and ultimately all ER+ MBC patients develop acquired resistance and progress on anti-hormonal therapy (Musgrove and Sutherland, 2009). The disadvantage for ESR1 mutated patients is that not much of what is offered currently seems to get in the way of their disease progressing. It is well documented that aromatase inhibitors are not effective for ESR1 mutated ER+, HER2-, MBC (Dustin, Gu and Fuqua, 2019). Patients are at a disadvantage if offered aromatase inhibitors when they have ESR1 mutated disease. Fulvestrant is currently the closest comparator to Elacestrant and requires injection in the buttocks, every two weeks for the first three doses and every month following

	that. The buttock injections take about 1-2 minutes and patients have said that they experience soreness and swelling for a few days after. Elacestrant appears to be tolerated generally well. Perhaps this is because patients who are taking the drug have already been exposed to side effects of anti-oestrogen therapy. One patient said, "This treatment is so easy and I feel pretty good". Another, "I have been on Orserdu since October and my scans have been very good and I am so grateful.". A few patients are already using Elacestrant as a combo replacing fulvestrant for ESR1 co-mutated disease and still tolerate it well, " Hormone blockers alone haven't worked for me since my 1st year of Stage IV disease, I am on year 6 now and take Elacestrant, Capivasertib and low dose Capecitabine. We are targeting ESR1 + AKT/PIK3 and hoping that will re-sensitise me to the oral chemo. My markers are accurate for me and are coming down, slow and steady." Also, "Combining is working well for me. Orserdu (elacestrant) and Truqap (capivasertib)". Some patients reported issues with nausea and muscle spasms on the monotherapy. ER+, HER2-, ESR1 mutated patients in the United Kingdom are concerned that they have no treatment available and that chemotherapy may not be effective for their ER+ disease. References: Dustin, D., Gu, G. and Fuqua, S.A. (2019) '*esr1* mutations in breast cancer', *Cancer*, **125**(21), pp. 3714–3728. doi:10.1002/cncr.32345.

	Musgrove, E.A. and Sutherland, R.L. (2009) 'Biological determinants of endocrine resistance in breast cancer', *Nature Reviews Cancer*, **9**(9), pp. 631–643. doi:10.1038/nrc2713.
9a. If there are advantages of Elacestrant over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does Elacestrant help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	9a. It is the first treatment to show clinical meaningful progression free survival for ESR1 mutated ER+ HER2- disease and includes co-existing PIK3CA/TP53/HER2-low and ESR1 mutant variants. Less time for patients to be spent in clinic and all that entails for fulvestrant. Portable pills allowing patients and hospital clinics/GP's/nurses to be released from the shackles of fulvestrant appointments. It is well documented that aromatase inhibitors are not an effective treatment for ESR1 mutated ER+, HER2-, MBC. 9b. Efficacy of this treatment for a substantial cohort of ESR1 mutated and co-mutated patients is the biggest advantage. 9c. Elacestrant is a pill so much easier to take.
10. If there are disadvantages of Elacestrant over current treatments on the NHS please describe these. For example, are there any risks with Elacestrant? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Generally, elacestrant seems well tolerated and is already used as combination treatment arm in trials and elsewhere in the world.
11. Are there any groups of patients who might benefit more from Elacestrant or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Being a pill, the responsibility of taking it does rely on the patient and therefore if a patient suffers from cognitive/dexterity impairments, they may need support at home. Patients with limited mobility may find it easier to take a medication in pill form and patients in general feel less anxious taking a pill in preference to the pain and discomfort of injections.
12. Are there any potential equality issues that should be taken into account when considering oestrogen	None noted.

receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment and elacestrant? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	Yes. The sub-group analysis of Elacestrant for ER+, HER2- MBC with ESR1-mutated tumours from the phase III EMERALD trial. This was analysed by prior duration of endocrine therapy plus CDK 4/6 inhibitor and in clinical subgroups. Bardia *et al.* (2024) confirmed in the phase III EMERALD sub group analyses that randomised ESR1 mutated patients with ER+, HER2- MBC, 1-2 prior lines of ET, mandatory CDK4/6i, and ≤ 1 chemotherapy associated with a clinically meaningful improvement in PFS consistent across all subgroups evaluated (PIK3CA; TP53; HER2-low; ESR1 D538G; ESR1 Y537S/N) for 345mg elacestrant compared to standard of care (aromatase inhibitor or fulvestrant). Reference:

	Bardia, A. *et al.* (2024) 'Elacestrant in ER+, HER2– MBC with *esr1*-mutated tumors: Subgroup analyses from the Phase III emerald trial by prior duration of endocrine therapy plus CDK4/6 inhibitor and in clinical subgroups', *Clinical Cancer Research* [Preprint]. doi:10.1158/1078-0432.ccr-24-1073.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Gap in current technology available to address common ESR1 mutations in metastatic breast cancer and considering all breast cancers are heterogeneous, there is an urgent need to move on from the majority of women receiving the same treatment as though all breast cancers were the same within a given subtype.
- Clinically meaningful improvement in PFS for ESR1 mutated metastatic breast cancer consistent across all subgroups evaluated (PIK3CA; TP53; HER2-low; ESR1 D538G; ESR1 Y537S/N) for 345mg elacestrant compared to standard of care (aromatase inhibitor or fulvestrant).
- Pill form offers patients a greater freedom, less appointment anxiety in comparison to pain and discomfort from injections of fulvestrant.
- Genomic testing of patient disease may better inform care for patients.
- The drug seems generally well tolerated by patients.

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Single Technology Appraisal

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment or caring for a patient with oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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Patient expert statement

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Part 1: Living with this condition or caring for a patient with oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment

Table 1 About you, oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment, current treatments and equality

1. Your name	Eleanor Pearce Willis
2. Are you (please tick all that apply)	☐ A patient with oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Breast Cancer Now
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☒ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations

Patient expert statement

	submission ☒ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☒ I have not completed part 2 of the statement
6. What is your experience of living with oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment? **If you are a carer (for someone with oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment on the NHS?	

7b. How do your views on these current treatments compare to those of other people that you may be aware of?	
8. If there are disadvantages for patients of current NHS treatments for oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment (for example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of elacestrant over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does elacestrant help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	
10. If there are disadvantages of elacestrant over current treatments on the NHS please describe these. For example, are there any risks with elacestrant? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from elacestrant or any who may benefit less? If so, please describe them and explain why	

Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment and elacestrant? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

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Single Technology Appraisal

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Clinical expert statement

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Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

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Part 1: Treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Mukesh Bindlish Mukesh
2. Name of organisation	East Suffolk & North Essex NHS Trust
3. Job title or position	Consultant Clinical Oncologist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment? ☐ A specialist in the clinical evidence base for oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes

7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NA
8. What is the main aim of treatment for oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	a. Stop progression of cancer and improve patients' quality of life. b. Improve long term overall survival. c. Delay the need for chemotherapy and associated side effects.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Improvement in patients' symptoms and reduction in size of tumour burden. In clinical practise, use of RECEIST for radiological assessment.
10. In your view, is there an unmet need for patients and healthcare professionals in oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment?	Yes. We currently have limited non-chemotherapy-based options. Both combination of Exemestane & Everolimus and Faslodex & Alpelesib associated with significant side effects.
11. How is oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Most patients are tested for PIK3CA mutation. In patients with endocrine sensitive disease (>12 months response to CDK4/6 inhibitors) with no PIK3CA mutation, exemestane & everolimus combination is used. For patients with PIK3CA mutation patients, Faslodex & Alpelesib combination is used. A small proportion of patients with high burden visceral disease, chemotherapy is also used. ESMO & NICE guidelines are commonly used in clinical practice. Some patients have access to single agent Faslodex or re-challenged with different CDK4/6 inhibitors.

	50% patients with ESR1 mutation would be suitable for oral therapy. Use of oral therapy will potentially help with capacity in chemotherapy units.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Elacestrant will be delivered and monitored in secondary care like most cancer therapies. We need liquid biopsy for ESR 1 testing to identify patients suitable for Elacestrant. This is currently not routinely done in breast cancer though lung cancer patients are having liquid biopsy and genome sequencing via NHS genomic hubs.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Elacestrant has shown a clinically significant improvement in PFS so likely to increase survival rates and delay the need for chemotherapy. The drug adverse events profile is also favourable so will improve health related quality of life over current care.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use?	The technology would be easier as it is an oral preparation. Major practical implication would be setting up the liquid biopsy for ESR1 testing.

(For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	ESR 1 testing
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Treatment regime would be oral so can be delivered in home care setting or outpatient setting without the need to access chemotherapy unit.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Elacestrant is an innovation in targeting the ESR 1 mutation which is one of the main drivers for endocrine resistance.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	No
20. Do the clinical trials on the technology reflect current UK clinical practice?	The trial use AI monotherapy or Faslodex monotherapy as comparator which is not current UK practice.

• If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Indirect comparison with exemestane & everolimus or Faslodex & Alpelesib would be more suitable. Use of real world data like Flatiron data would be helpful.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA421 and TA816?	No
23. How do data on real-world experience compare with the trial data?	New drug so very limited real world data.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.	No

Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	
25. Elacestrant is indicated for the treatment of people who have been through the menopause, and men, with oestrogen receptor-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least 1 line of endocrine therapy including a CDK 4/6 inhibitor. Where in the treatment pathway would you expect to use elacestrant?	Patients with HR, Her-2 negative locally advanced/metastatic breast cancer who have progressed on CDK4/6 inhibitors after 12 months and carry a ESR 1 mutation.
26. When would you expect diagnostic testing for the ESR1 mutation to happen?	Post CDK4/6 progression.
27. What are the relevant comparators for elacestrant?	Exemestane & Everolimus Faslodex & Alpelesib

28. Are clinical outcomes likely to be different depending on whether the locally advanced or metastatic breast cancer is oestrogen receptor-positive or progesterone receptor-positive?	No

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Elacestrant is an effective oral therapy suitable for patients who have progressed on CDK4/6 inhibitors and carry a ESR 1 mutation.

It delays the need for chemotherapy and associated side effects

It can have a positive impact on patients' quality of life by decreasing tumour burden with favourable safety profile.

Will help with capacity issues seen in chemotherapy units

Allow setting up use of liquid biopsy in breast cancer pathways.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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Single Technology Appraisal

Elacestrant for treating oestrogen receptor-positive HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 29 July 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Description of uncertainties - clinical effectiveness

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG urges caution in the interpretation of clinical effectiveness results, with one reason being small sample sizes, notably in *post hoc* subgroup 2. Based on the NICE final scope, the Company presented a *post hoc* subgroup analysis to enable comparison with alpelisib + fulvestrant, a comparator selected by NICE. Consequently, this subgroup has a small sample size. **Section 1.2, Issue 1, page 12** "*The EAG urges caution in the interpretation of these results due to:* • *Small sample sizes, notably for post hoc subgroup 2 (13% of randomised patients).*"	The Company proposes that the EAG amend the wording throughout the report to reflect that this subgroup was selected to enable comparison with a comparator in the final scope from NICE. For example: "The EAG urges caution in the interpretation of these results due to: • *Small sample sizes, notably for post hoc subgroup 2 (13% of randomised patients), <u>although we note that this subgroup was presented to enable comparison with a comparator defined in the final scope from NICE</u>.*"	To justify the Company's rationale for including this small post-hoc subgroup; to enable comparison with a comparator selected by NICE in the final scope.	Not a factual inaccuracy, no change made. The size of the post hoc sub-groups was not only influenced by the elements of the NICE scope (e.g. comparators) but also by amendments to the scope made by the company in their decision problem. These included restricting the patient population to those with longer exposure (i.e. ≥12 months) to prior ET + CDK4/6i.), and restricting the comparator treatments to everolimus + exemestane and alpelisib + fulvestrant. It would be misleading to not mention the company's role in defining the subgroups.

The EAG urges caution in the interpretation of clinical effectiveness results based on imbalances in baseline characteristics affecting post hoc subgroup 2, which might bias results in a way that favours elacestrant. The EAG makes this statement in reference to patients receiving elacestrant, potentially having more advanced disease, due to a higher proportion of adverse prognostic factors. This is contrary to clinical feedback the Company has received, where these patients would be expected to do less well on treatment. **Section 1.2, Issue 1, page 12** *"Some evidence of selection bias due to imbalances in baseline characteristics…suggesting slightly more advanced cancer than the comparator arm.*	The Company proposes that the wording throughout the report is amended to be factual only, and not to claim a direction of effect. The Company agrees that there are potential imbalances in the baseline characteristics relating to adverse prognostic factors, but the impact of these potential imbalances on the clinical efficacy and safety of elacestrant is not certain based on the clinical feedback received by the Company and the EAG. See the Company's suggestions for each example respectively: • *"Some evidence of selection bias due to imbalances in baseline characteristics…suggesting slightly more advanced cancer than the comparator arm. <u>The impact of these imbalances is unclear.</u>"* • *"The above baseline characteristics indicate that patients in the elacestrant arm of post-hoc subgroup 2 (dual mutation)…compared to*	The Company disagree that these imbalances favour elacestrant. The Company believe based on clinical feedback that the opposite to be true, and that the patients in the elacestrant group are harder to treat as they have a higher proportion of adverse prognostic factors, and therefore that these imbalances might underestimate the clinical efficacy and safety of elacestrant.	The expectation is that EAG's not only point out where bias is apparent but also to estimate the likely magnitude and direction of the bias. NICE appraisal committees find it helpful to understand the impact of any bias to inform their decision making. Therefore, it is entirely within our remit to point this out. With hindsight, however, we agree that the baseline imbalances in this particular case do not necessarily imply over-estimation of the clinical efficacy and safety of elacestrant. Given the level of uncertainty it is more appropriate to consider the impact of imbalances as being unclear. We

Potentially this might over-estimate the clinical efficacy and safety of elacestrant." Variations of this point are made at multiple points in the EAG report, including, but not limited to, the following: **Section 3.2.1.2, page 39** *"The above baseline characteristics indicate that patients in the elacestrant arm of post-hoc subgroup 2 (dual mutation)…compared to patients in the SOC arm. Patients in the elacestrant arm of post-hoc subgroup 2 (dual mutation) could therefore benefit from elacestrant more than they would do otherwise."* **Section 3.2.4, Table 8, page 50** *"The post hoc status of the subgroup analysis means the results are at increased risk of bias, potentially over-estimating the clinical effectiveness of elacestrant."*	*patients in the SOC arm. <u>The impact of these imbalances is unclear.</u>"* • *"The post hoc status of the subgroup analysis means the results are at increased risk of bias, <u>although the impact of this is unclear</u>."*		have made the amendments suggested.

Issue 2 ESR1 mutation testing

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In the examples below, the Company would like to suggest some slight amendments to the text to provide further clarity on the issues with the detection of ESR1-mut using tissue biopsy (as proposed by NHS England), and why using ctDNA (as proposed by the Company) is better suited to the detection of ESR1-mut: **Section 1.4, Issue 5, page 17** *"Genetic testing for breast cancer is routine prior to treatment, using a tissue sample and digital PCR assay. However, as ESR1 is an acquired mutation,*	The Company proposes the text be amended to the following for each example respectively: • "*Genetic testing for breast cancer is routine prior to initiating or during frontline treatment, using a tissue sample (most often archival from diagnosis) and digital PCR assay. However, as ESR1 is an acquired mutation, analysis and an archival tissue sample will not be accurate in detecting an ESR1 mutation. Tissue biopsy could be used to test for ESR1-mut when treatment with elacestrant is being considered.*	The Company would like to thank the EAG for recognising the importance of ctDNA to detect ESR1 mutations and the limitations of tissue biopsy at progression. The Company would like to ensure that the report accurately reflects the issues that are specific to ESR1-mut testing using tissue biopsy (as proposed by NHS England) as this will be important in whether patients are able to access elacestrant in a timely manner. The acquired nature of the mutation resulting from exposure to endocrine treatment means that historical tissue samples will not detect ESR1-mut. Even if a tissue	We thank the company for these suggestions. However, we believe the text in the EAG report is sufficiently detailed to convey the points the company wishes to emphasise. For this reason, coupled with the EAG's time limitations, we have not incorporated the suggestions.

analysis of the primary tumour sample may not be accurate. Digital PCR could be used to test for the ESR1 mutation when treatment with elacestrant is being considered. However, this would require a repeat biopsy, which may not reflect disease status due to tumour heterogeneity, and there is potential for delay to the start of treatment." **Section 3.2.1.1, page 37** *"The proposed test for the NHS would utilise a tissue sample, either a primary tumour sample, which is limited due to being a historic sample, or a single site repeat biopsy, which is limited by the potential to not fully reflect disease status due to within tumour heterogeneity."* **Section 4.2.6.5, page 96** "*However, this approach has disadvantages,*	*However, this would require r<u>epeat tissue biopsies that are not routine in the NHS following relapse after CDK4/6 inhibitors</u>, may not reflect disease status due to tumour heterogeneity, and there is potential for delay to the start of treatment.* • *"The proposed test for the NHS would utilise a tissue sample, either a primary tumour sample, <u>which will not be accurate in detecting ESR1-mutation as ESR1 is an acquired mutation</u>, or a single site repeat biopsy <u>that should occur at progression CDK4/6i +ET – this is infrequent in the NHS and</u> is limited by the potential to not fully reflect disease status due to within tumour heterogeneity and by*	biopsy is done at progression, which is rare in the NHS, they may not fully reflect disease status due to within-tumour heterogeneity and may delay start of the treatment.	

including either reliance on a historical tissue sample or a single site repeat biopsy, which may not reflect disease status due to tumour heterogeneity."	*significant capacity issues in the NHS to perform the biopsy."* • "*However, this approach has disadvantages, including either reliance on a historical tissue sample, which will not be accurate in detecting ESR1-mutation as ESR1 is an acquired mutation, or a single site repeat biopsy, which may not reflect disease status due to tumour heterogeneity.*"		
The text below suggests all other NHS GLHs are exploring the Marsden360 assay. Whereas from the Company's interactions, other GLHs are developing a range of similar approaches but not necessarily the same assay as Marsden360 assay. **Section 1.4, Issue 5, page 18**	The Company proposes that the wording throughout the report is amended to reflect that other NHS GLHs are exploring similar approaches. e.g. the Company proposes the text be amended to the following: *"North Thames NHS Genomic Laboratory Hub (GLH) currently provide a ctDNA test that can identify the ESR1 mutation (Marsden360 assay), and we*	To accurately reflect that a range of different approaches are currently being explored and developed by GLHs across the country.	We have amended the text to say *"we understand that other NHS GLHs are exploring this or a similar approach"* throughout the report.

"North Thames NHS Genomic Laboratory Hub (GLH) currently provide a ctDNA test that can identify the ESR1 mutation (Marsden360 assay), and we understand that other NHS GLHs are exploring this approach." Further instances – not exhaustive – are as follows: **Section 4.2.6.5, page 97** *"We understand that a number of NHS GLHs are currently exploring this delivery model for ctDNA testing."* **Section 6.4, page 128** *"ctDNA testing is currently available from the North Thames NHS GLH using the Marsden360 assay. We understand that a number of NHS GLH's are exploring this delivery model for ctDNA testing, and that the cost could fall if NGS panel*	*understand that other NHS GLHs are exploring similar approaches that will enable ESR1-mut testing on ctDNA.*		

testing were to be introduced for ESR1 and additional treatment targets as they become available."			
The text below does not clearly state that the proposed test mentioned is that proposed by the NHS, not by the Company. **Section 3.2.1.1, page 37** The EAG on page 37 writes: *"The EAG clinical expert believed that the proposed test to identify ESR1-mutation status in the NHS is not the same, and has disadvantages, compared to the test used in the EMERALD trial."*	The Company proposes that the text is amended to: "*The EAG clinical expert believed that the <u>test proposed by NHS England</u> to identify ESR1-mutation status in the NHS is not the same, and has disadvantages, compared to the test used in the EMERALD trial."*	To clarify that this is the position of the NHS, not the Company. The Company notes that while this statement is the EAG clinical expert's opinion, it makes it sound like this is the test proposed by the Company. The Company wants to clarify that this is the test being proposed by the NHS, not that proposed by the Company.	We do not agree that statement implies it is the company's proposal. We believe the clinical expert's comment relates to an assumption that NHS England were proposing a PCR test on a tissue sample, rather than ctDNA tests (e.g. the Marsden 360 vs. the assay used in the trial).
The Company would like to seek clarity on whether the price proposed by NHS England is for ESR1 mutations testing by droplet PCR or NGS on ctDNA.	The Company proposes the sentence be extended to provide further clarity on whether the proposed price by NHS England is for ESR1-mut only by droplet PCR.	The cost included in the model by the Company is for droplet PCR on ctDNA. This cost is included as it would be used to identify ESR1 mutations only. As highlighted by the EAG, an NGS panel on ctDNA can	Not a factual inaccuracy. We report all of the information that we have about the basis of the NHS Genomics indicative cost of future NGS ctDNA testing after the quoted text in

Section 4.2.6.5, page 97 "In response to a request from NICE, the NHS Genomic Medicine Service (GMS) provided estimates of the possible cost of ctDNA tests for ESR1 mutation in the NHS. They suggested that for the purpose of modelling the impact on the NHS, the cost of providing this testing would be in the region of [redacted]"		identify a wide range of mutations for other treatments and could be argued that the cost of the test is removed. The Company position is that if the cost is included in the model it should be for droplet PCR. It is therefore important the report is specific on what the costs used in the report are.	section 4.2.6.5 page 97. We do not have any further detail. The EAG base case uses the company's estimated cost for droplet PCR on ctDNA (£300 per test), and we report scenario analysis with the NHS Genomics indicative cost for NGS panel ctDNA ([redacted] per test), and other cost assumptions in EAR Tables 43 and 44. No changes made.

Issue 3 Amendments to report text for greater clarity

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The text identified below does not list some specific exclusion criteria relevant to	The Company proposes that some additional text is added to the end of the statement:	To provide clarity about the exclusion criteria specific to the UK population.	The proposed additional text has been added.

the UK patients in the EMERALD trial: **Section 3.2.1.1, Table 5, page 35** *"Patients with symptomatic metastatic visceral disease or any of the following cardiovascular events…coagulopathy (thrombosis), and cerebrovascular accident"*	*"Patients with symptomatic metastatic visceral disease or any of the following cardiovascular events…coagulopathy (thrombosis), cerebrovascular accident <u>and in the UK patients were excluded if they had a QTcF of ≥450 msec</u>"*		
On page 37 of the report, the EAG state that they are unclear whether all patients with visceral metastases at baseline were asymptomatic from these metastases, and therefore met the EMERALD trial inclusion criteria. However, this is stated in the trial exclusion criteria. **Section 3.2.1.1, page 37** *"It is unclear to the EAG whether all these patients had asymptomatic visceral metastasis, and therefore met*	The Company proposes that if the EAG are satisfied with the below clarification, that the statement is removed from the report. The CSR details the exclusion criteria specific to visceral metastases: *"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.*	The exclusion criteria from the CSR make it clear that all patients with visceral metastases who were included in the EMERALD trial will have been asymptomatic. We hope this reassures the EAG.	Considering clarification from the company, the statement on page 37 has been removed. Associated text on page 36 has also been amended (i.e. "three issues" amended to "two issues" and the first issue of three deleted).

the inclusion criteria for the trial, or not." The Company would like to provide some clarification to reassure the EAG that all patients with visceral metastases at baseline were asymptomatic.	*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 nonenzyme inducing anticonvulsant regimen (see Appendix 8 of the protocol in Appendix 16.1.1)*" - CSR Section 9.3.2, page 35)		
The sentence below is misleading. It introduces the economic model, when the section is not about the economic model, and the	The Company proposes that the sentence is removed.	To ensure that there is no confusion around whether the issues raised are to do with the data used in the economic	The sentence has been removed as suggested.

issues raised do not apply to the economic model. **Section 3.2.5.3, page 55** "*The HRQoL outcome used in the economic model was the EQ-5D-5L.*"		model, or the data presented in the clinical efficacy section.	
The point below does not speak to a specific treatment. The Company agree that 5-year survival for everolimus + exemestane treated patients is expected to be around 5%. However, clinical opinion to the Company anticipates greater 5-year survival for elacestrant in comparison to everolimus + exemestane. **Section 4.2.4.2, page 79** *"Expert advice to the EAG is that 5-year survival in this population is likely to be around 5%, and that although there may well be a small proportion of patients who gain a long-term benefit, this is as yet untested. We therefore conclude that the*	The Company proposes that the sentence is amended to be more specific about the treatments being referred to here.	To provide clarity on the expert opinion provided to the EAG regarding the treatment-specific long-term comparative estimates.	Not a factual error. However, for clarity we have specified that the 5% 5-year survival estimate relates to current treatment, and that although there may well be a small proportion of patients who gain a long-term benefit with elacestrant, this is as yet untested.

company's base case log-logistic OS extrapolation for elacestrant is overly optimistic given the current evidence base."			
The statement below could be misleading as the reporting time for digital PCR may vary from one GLH to the other and the turnaround time for "mutation specific molecular pathology tests" is listed as 14 days on the North Thames GMS website. Repeat tissue biopsy is probably the biggest factor influencing delay for the treatment. This is related to the need for patients to be assigned to a surgical list and then the time for pathology to prepare the sample. Clinical feedback is that it is currently taking more than 4 weeks to obtain tissue biopsy results from archival tissue in certain regions. The addition of the need of a new biopsy will extend this time frame even further	The Company proposes the text be amended to the following: "*Repeat <u>tissue</u> sample collection and reporting of the result might delay the start of treatment.*"	To truly reflect that repeat tissue biopsy may delay start of the treatment	Not a factual accuracy. It is clear from the context that this sentence refers to tissue biopsy.

Section 4.2.6.5, page 96 "*Repeat sample collection and reporting of the result might delay the start of treatment, as the current reporting time for digital PCR is about a week.*"			
The Company would like to seek clarity on the following statement to ensure correct understanding. In particular: • Are the EAG suggesting the cost-effectiveness of elacestrant produced by the model is better or worse than it should be for subgroup 2? • Are there any implications on the cost-effectiveness for subgroup 1? **Section 1.2, Issue 1, page 13**	The Company proposes the sentence be extended to provide further clarity on the EAG's expected effect on the cost-effectiveness estimates.	To provide clarity on the EAG's expected effect on cost-effectiveness estimates	We have amended the text to say "This is uncertain currently."

"Possible over-estimation of cost effectiveness in patients with dual mutation"			
The sentence below does not clarify that the Company made corrections at the clarification stage. **EAG comment on resources and costs, page 98** *"The EAG identified some minor errors in resource use costs (physiotherapy), subsequent treatment costs (paclitaxel 100 mg list price, total costs per treatment in CS Table 74), and adverse events (AE frequency in CS Table 63)"*	The Company proposes that a sentence is added to the end of the statement: *"The EAG identified some minor errors in resource use costs (physiotherapy), subsequent treatment costs (paclitaxel 100 mg list price, total costs per treatment in CS Table 74), and adverse events (AE frequency in CS Table 63). <u>These errors were corrected by the Company at the clarification stage.</u>"*	To clarify that the Company addressed the errors highlighted by the EAG at the clarification stage and the Company ICERs presented in the EAR include these corrections.	The EAG mentioned in sections 4.2.6.4 and 5.3.1 that the company had amended these parameters. We agree to include this information on the EAG comment on resource and costs in page 98

Issue 4 Incorrect information

Description of problem	**Description of proposed amendment**	**Justification for amendment**	
The description of the evidence used to support the claim that the population of patients with ER+/HER2-	The Company proposes the text be amended to the following:	To correctly list the type of evidence used (not all were RCTs), and the various studies that were used to support the	We have added the suggested citations to the studies

ESR1-mutated advanced/metastatic breast cancer experience faster disease progression and poorer survival than those without ESR1-mutation is incomplete and not fully accurate: **Section 2.2.1, page 22** *"The evidence cited in support of this claim comes from the company's analysis of randomised controlled trials (RCTs) of endocrine therapy in advanced hormone receptive / HER2 negative breast cancer (the MAINTAIN trial; the SoFEA and EFECT trials)."*	"*The evidence cited in support of this claim comes from the Company's analysis of publicly available studies of endocrine therapy in advanced hormone receptor positive breast cancer (the BOLERO-2 trial, Clatot et al, the MAINTAIN, BYLieve, SoFEA and EFECT trials).*"	statement about ESR1-mutations in the Company submission.	
The wrong page number was used in the below statement when referring to the Company Submission **Section 2.2.2, page 22**	The Company proposes the text be amended to the following: "(*CS page 14, reproduced from the Summary of Product Characteristics*)."	To ensure the correct page number is stated.	Corrected

"(CS page 15, reproduced from the Summary of Product Characteristics)."			
An inaccurate statement around the current pathway for advanced/metastatic ER+/HER2- breast cancer is made. Patients can receive more than three successive lines of therapy as their cancer progresses. **Section 2.2.3.1, page 23** *"As can be seen, patients can receive up to three successive lines of therapy as their cancer progresses."*	The Company proposes that the statement is removed as it is misleading.	To correctly reflect the treatment pathway, as confirmed by the EAG's clinical expert, which includes more than three successive lines of therapy Figure 6 in the CS was to represent the positioning of elacestrant in the current treatment pathway but in no circumstances to indicate that patients would only receive up to 3 lines of therapy. We agree with the EAG's clinical expert, some patients with hormone responsive cancer who progress on second line therapy might switch to third line hormone therapy, with whichever drugs they haven't already received. In addition, as per ESMO guidelines, sequential chemotherapy can also be considered as a treatment option; the clinical	We have removed the words "up to three"

		advice to the EAG noted capecitabine and eribulin as options.	
An inaccurate statement around the pattern of results seen by ESR1 mutation status is made. **Section 2.3, page 29** *"The EAG also notes there is a similar pattern in the results irrespective of whether patients had the ESR1 mutation."*	The Company proposes the text be amended to the following: "*The EAG also notes there is a similar pattern in the results in the <u>All-patient population</u>.*"	To correctly reflect results of a subgroup analysis presented at ASCO 2023, where patients with ESR1-mut-nd tumours were shown to benefit from elacestrant only if the duration of CDK4/6i was <6 months.	We have amended the wording as suggested, though the original wording is not contradictory.
The list of secondary outcomes informing the economic model is misleading, as not all were EMERALD trial outcomes, some were analysed for the economic model: **Section 3.2.1.1, page 36** *"Overall survival, time to treatment discontinuation, EQ-5D-5, adverse events (Grade ≥ 3c occurring in ≥2% of patients)"*	The Company proposes the text be amended to delete the outcomes that were not specific EMERALD trial outcomes: *"Overall survival, EQ-5D-5L and adverse events"*	To accurately reflect the secondary outcomes from the EMERALD trial that were used to inform the economic model	Thank you for highlighting this error. The text has been amended as suggested.

A statement regarding the treatment history and exposure in the comparator arm of the EMERALD trial is misleading: **Section 3.2.1.1, page 37** *"Some patients in the EMERALD trial comparator arm had prior exposure to a non-steroidal aromatase inhibitor and were assigned to receive another in the trial. Switching from one drug to another that works in the same way is rarely done in clinical practice as the likelihood of overcoming resistance would be expected to be very low"*	The Company proposes the statement is either removed or edited to reflect the below as it is misleading: *"Patients in the EMERALD trial could also receive a steroidal aromatase inhibitor following a non-steroidal one and vice versa, although this was not the preferred option. A few patients received several lines of therapy and may have received a similar AI in one of these prior lines, but not in the line directly prior to starting the trial. Switching from one drug to another that works in the same way is rarely done in clinical practice as the likelihood of overcoming resistance would be expected to be very low."*	To accurately reflect the rationale for treatment allocation in the EMERALD trial and the patients' prior treatment history. SOC treatment was per investigator's choice of fulvestrant, anastrozole, letrozole, or exemestane monotherapy and dosed according to the labelling. This guidance recommended the use of a different endocrine therapy than the patient had received previously. Specifically, fulvestrant was recommended for patients who had not previously received fulvestrant, and aromatase inhibitors were selected based on prior exposure. Detailed guidance for choice of SOC agent is provided in the Protocol (online only), as detailed in the Data Supplement (Bidard *et al*. 2022).	The statement of concern to the company is the opinion of the EAG's clinical expert (it is one of the bullet points relating to "Additional issues regarding comparators the EAG clinical expert highlighted"). The EAG believes it would be inappropriate to amend the wording as suggested by the company as it would not reflect the expert's opinion. The EAG have, however, added the company's suggested text *after* the expert's statement: "*The company state that while patients in the EMERALD trial could also receive a steroidal aromatase inhibitor following a non-steroidal one and vice versa, this was not the preferred option. A few patients received several lines of therapy and may have received a similar AI in one of these prior lines, but*

			not in the line directly prior to starting the trial"
In Table 8 of the EAG report, only the modified per-protocol patient numbers are given rather than both the per-protocol and modified per-protocol patient numbers, but they are stated as the per-protocol numbers: **Section 3.2.4, page 45** *"Per protocol and modified per protocol: defined as…(All PP patients: N=461; ESR1-mut N=219)*"	The Company proposes that the per-protocol patient numbers be added with the text amended to the following: *"Per protocol and modified per protocol: defined as…(All PP patients: N=464; ESR1-mut PP: N=221; all mPP patients: N=461; ESR1-mut mPP: N=219)*"	To accurately reflect the per-protocol and modified per-protocol patient numbers.	Thank you for highlighting this error. The text has been amended as suggested.
There is an adverse event missing from the list of most common adverse events for SOC for all patients. **Section 3.2.5.5, page 58** "*The most common adverse event for the SOC group differed between patient populations: for all patients nausea (19.1%), for ESR1-mut…*"	The Company proposes the text be amended to the following to include the missing adverse event: "*The most common adverse event for the SOC group differed between patient populations: for all patients nausea and fatigue (both 19.1%), for ESR1-mut…*"	To fully reflect all most common adverse events for SOC.	Thank you for highlighting this error. The text has been amended as suggested.

The sentence below contains an error; the AE disutility estimates are not used in the Company base case (as is acknowledged elsewhere in the EAR). **Section 4.2.5.1, page 90** *"These studies provided the AE disutilities estimates used in the company's base case…"*	The Company proposes that the sentence is reworded to: *"These studies provided the AE disutilities estimates used in the Company scenario analysis…"*	To ensure there is no confusion around the Company base-case assumption.	Thank you for highlighting this error. As suggested, we have amended the text on section 4.2.5.1, page 90.
In the statement below, the ICER is incorrect: **Section 6.1.1.2, page 110** "*The EAG scenario with ALP+FUL TTD estimated assuming a 0.5 hazard ratio relative to the ALP+FUL PFS curve resulted in an ICER of £7,094 per QALY (elacestrant not dominant).*"	The Company proposes the text be amended to the following: "*The EAG scenario with ALP+FUL TTD estimated assuming a 0.5 hazard ratio relative to the ALP+FUL PFS curve resulted in an ICER of £4,362 per QALY (elacestrant cost-effective but not dominant).*"	To reflect the correct ICER.	Thank you for highlighting this error. We have amended the ICER for this scenario.
The change in ICER is incorrect in the statement below: **Section 6.1.4, page 112**	The Company proposes the text be amended to the following: *"For subgroup 1, this scenario increased the ICER by £231."*	To reflect the correct change in the ICER.	Thank you for highlighting this error. We have amended the ICER increment for the associated scenario.

"For subgroup 1, this scenario increased the ICER by £175."			
This statement claims that elacestrant is not cost-effective when the generalised gamma extrapolation is chosen to inform elacestrant OS. However, this scenario could not be performed as the generalised gamma model did not converge to the elacestrant OS data for subgroup 2: **Appendix 5, page 155** "*Only one scenario is not cost-effective, with a negative NMB of -£7,181 (generalised gamma as OS extrapolation for elacestrant).*"	The Company proposes that the text be amended to the following: "*All scenarios are cost-effective, though one scenario could not be performed owing to a lack of model convergence (generalised gamma as OS extrapolation for elacestrant).*"	To reflect that this scenario could not be performed due to the lack of model convergence to the data.	Thank you for noting this error. We have amended the paragraph as suggested.

Confidentiality markup

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 3.2.1.2, page 38	"A [redacted] proportion of the elacestrant arm received fulvestrant as prior therapy for advanced or metastatic disease compared to the SOC arm ([redacted])"	"A [redacted] proportion of the elacestrant arm received fulvestrant as prior therapy for advanced or metastatic disease compared to the SOC arm ([redacted])"	We have highlighted the information as confidential.
Section 3.2.1.2, page 39	"A [redacted] proportion of the elacestrant arm received mammalian target of rapamycin (mTOR) inhibitor as prior therapy for advanced or metastatic disease compared to the SOC arm ([redacted])"	"A [redacted] proportion of the elacestrant arm received mammalian target of rapamycin (mTOR) inhibitor as prior therapy for advanced or metastatic disease compared to the SOC arm ([redacted])"	We have highlighted the information as confidential.
Section 3.2.1.2, page 39	"Median age was slightly [redacted] in the elacestrant arm than in the SOC arm ([redacted])."	"Median age was slightly [redacted] in the elacestrant arm than in the SOC arm ([redacted])."	We have highlighted the information as confidential.
Section 3.2.1.2, page 39	"A [redacted] proportion of participants in the elacestrant arm has visceral metastasis (including lung, liver, brain, pleural, and peritoneal involvement) compared to the SOC arm ([redacted])"	"A [redacted] proportion of participants in the elacestrant arm has visceral metastasis (including lung, liver, brain, pleural, and peritoneal involvement) compared to the SOC arm ([redacted])"	We have highlighted the information as confidential.
Section 3.2.1.2, page 39	"A [redacted] proportion of the elacestrant arm received mTOR inhibitor as prior therapy for	"A [redacted] proportion of the elacestrant arm received mTOR inhibitor as prior therapy for	We have highlighted the information as confidential.

	advanced or metastatic disease compared to the SOC arm ([redacted])"	advanced or metastatic disease compared to the SOC arm ([redacted])"	
Section 3.2.1.2, page 39	"In the advanced or metastatic setting a [redacted] proportion of the elacestrant arm received one prior line of endocrine therapy compared to the SOC arm ([redacted]), and a [redacted] proportion of the elacestrant arm received two prior lines of endocrine therapy compared to the SOC arm ([redacted])."	"In the advanced or metastatic setting a [redacted] proportion of the elacestrant arm received one prior line of endocrine therapy compared to the SOC arm ([redacted]), and a [redacted] proportion of the elacestrant arm received two prior lines of endocrine therapy compared to the SOC arm ([redacted])."	We have highlighted the information as confidential.
Section 3.2.1.2, page 39	"The above baseline characteristics indicate that patients in the elacestrant arm of post-hoc subgroup 2 (dual mutation) were [redacted] compared to patients in the SOC arm"	"The above baseline characteristics indicate that patients in the elacestrant arm of post-hoc subgroup 2 (dual mutation) were [redacted] compared to patients in the SOC arm"	We have highlighted the information as confidential.
Section 3.2.2, page 42	"Second, there is a difference in the total number of patients with ESR1-mut enrolled in [redacted]; CSR Table 14.1.1.2) of the [redacted] countries and those that had a baseline EQ-5D-5L score (CSR Table 14.2.6.4.1). In total [redacted] ESR1-mut patients were enrolled from these [redacted] countries, with [redacted] assigned to elacestrant and [redacted] to SOC, yet baseline EQ-5D-5L index scores are only available for [redacted] patients in each arm (CSR Table 14.1.1.2	"Second, there is a difference in the total number of patients with ESR1-mut enrolled in [redacted]; CSR Table 14.1.1.2) of the [redacted] countries and those that had a baseline EQ-5D-5L score (CSR Table 14.2.6.4.1). In total [redacted] ESR1-mut patients were enrolled from these [redacted] countries, with [redacted] assigned to elacestrant and [redacted] to SOC, yet baseline EQ-5D-5L index scores are only available for [redacted] patients in each arm (CSR Table 14.1.1.2	We have highlighted the information as confidential.

	and CSR Table 14.2.6.4.1). It is unclear to the EAG why there is this discrepancy."	and CSR Table 14.2.6.4.1). It is unclear to the EAG why there is this discrepancy."	
Section 3.2.4, Table 8, page 50	"Baseline characteristics…there was a [redacted] percentage of patients in the elacestrant arm with visceral metastases. Likewise, a [redacted] proportion of elacestrant patients previously had two lines of endocrine therapy in the advanced/metastatic setting, and [redacted] had received prior adjuvant therapy. This suggests that patients treated with elacestrant were in a [redacted] than was the case for patients receiving standard of care endocrine monotherapy."	"Baseline characteristics…there was a [redacted] percentage of patients in the elacestrant arm with visceral metastases. Likewise, a [redacted] proportion of elacestrant patients previously had two lines of endocrine therapy in the advanced/metastatic setting, and [redacted] had received prior adjuvant therapy. This suggests that patients treated with elacestrant were in a [redacted] than was the case for patients receiving standard of care endocrine monotherapy."	We have highlighted the information as confidential.
Section 3.2.5.2, page 55	"There was no difference in the hazard rate of death for elacestrant compared to SOC for either post-hoc subgroup 1 (stratified HR [redacted], 95% CI [redacted] to [redacted]; p=[redacted]) or subgroup 2 (stratified HR [redacted], 95% CI [redacted] to [redacted]; p=[redacted])."	"There was no difference in the hazard rate of death for elacestrant compared to SOC for either post-hoc subgroup 1 (stratified HR [redacted], 95% CI [redacted] to [redacted]; p=[redacted]) or subgroup 2 (stratified HR [redacted], 95% CI [redacted] to [redacted]; p=[redacted])."	We have highlighted the information as confidential.
Section 3.2.5.5, page 58	"The most common adverse event for patients receiving elacestrant was nausea, which was consistent for all patients, ESR1-mut subgroup, and post-hoc subgroups 1	"The most common adverse event for patients receiving elacestrant was nausea, which was consistent for all patients, ESR1-mut subgroup, and post-hoc subgroups 1	We have highlighted the information as confidential.

	and 2 (35.0%, 34.8%, 38.5% and [redacted] respectively; see Table 13 and Table 14).”	and 2 (35.0%, 34.8%, 38.5% and [redacted] respectively; see Table 13 and Table 14).”	
Section 3.2.5.5, page 58	“The most common adverse event for the SOC group differed between patient populations: for all patients nausea (19.1%), for ESR1-mut subgroup fatigue (19.8%), for post-hoc subgroup 1 [redacted] and post-hoc subgroup 2 [redacted]”	“The most common adverse event for the SOC group differed between patient populations: for all patients nausea (19.1%), for ESR1-mut subgroup fatigue (19.8%), for post-hoc subgroup 1 [redacted] and post-hoc subgroup 2 [redacted]”	We have highlighted the information as confidential.
Section 3.2.5.5, page 58	“The proportion of patients experiencing adverse events with a severity grade ≥ 3 was similar between elacestrant and SOC for all patients, ESR1-mut subgroup, [redacted] (see Table 13 and Table 14)”	“The proportion of patients experiencing adverse events with a severity grade ≥ 3 was similar between elacestrant and SOC for all patients, ESR1-mut subgroup, [redacted] (see Table 13 and Table 14)”	We have highlighted the information as confidential.
Section 3.2.5.5, page 58	“The proportion of patients who experienced adverse events leading to dose interruption was greater in the elacestrant group compared to the SOC groups for all patients, ESR1-mut subgroup, [redacted] (see Table 13 and Table 14).”	“The proportion of patients who experienced adverse events leading to dose interruption was greater in the elacestrant group compared to the SOC groups for all patients, ESR1-mut subgroup, [redacted] (see Table 13 and Table 14).”	We have highlighted the information as confidential.

<table>
<tr>
<td>Section 3.2.5.5, Table 14, page 60</td>
<td>
Table 14 Summary of adverse events for post-hoc subgroups 1 (ESR1 mutation) and 2 (dual mutation)
<table>
<tr><th rowspan="2">Adverse event (AE)</th><th colspan="2">Post-hoc subgroup 1 (ESR1 mutation)</th><th colspan="2">Post-hoc subgroup 2 (dual mutation)</th></tr>
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<tr><td>Grade ≥3 in ≥ 2% of patients</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>AE leading dose interruption</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td colspan="5">AE reported in ≥ 10% of patients in either trial arm</td></tr>
<tr><td>Nausea</td><td>30 (38.5)</td><td>11 (14.7)</td><td>[redacted]</td><td>[redacted]</td></tr>
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Source: Partly reproduced from CS Appendix E Table 11, Table 12, Table 15 and Table 16
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<tr>
<td>Section 4.2.2.1, page 73</td>
<td>“For the base case economic analysis, the company used patient characteristics from EMERALD for both subgroups: [redacted] with mean ages [redacted] years for</td>
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</tr>
</table>

	subgroup 1 and [redacted] years for subgroup 2 (CS Table 39)."	subgroup 1 and [redacted] years for subgroup 2 (CS Table 39)."	
Section 7.1, page 129	"The proportion of females in the patient population: [redacted] (CS Table 39)."	"The proportion of females in the patient population: [redacted] (CS Table 39)."	We have highlighted the information as confidential.

External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Elacestrant for treating oestrogen receptor-positive, HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]

Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
Authors	Emma Maund, Research Fellow, Evidence synthesis Marcia Takahashi, Research Fellow, Health economics Joanne Lord, Professorial Research Fellow, Health economics Jonathan Shepherd, Principal Research Fellow, Evidence synthesis
Correspondence to	Dr Jonathan Shepherd Southampton Health Technology Assessments Centre (SHTAC) School of Healthcare Enterprise and Innovation University of Southampton Alpha House, Enterprise Road, University of Southampton Science Park, Southampton SO16 7NS www.southampton.ac.uk/shtac

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We also thank:

- Lois Woods, Senior Research Assistant, Southampton Health Technology Assessments Centre (SHTAC) for performing literature searching and critically appraising search strategies.

Declared competing interests of the authors and advisors

The authors declare none

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Maund, E; Takahashi, M; Lord, J; Shepherd, J. Elacestrant for treating oestrogen receptor-positive, HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]. A Single Technology Appraisal. Southampton Health Technology Assessments Centre, 2024.

Contributions of authors

Emma Maund critically appraised the clinical effectiveness systematic review, and drafted the report; Marcia Tomie Takahashi critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report. Joanne Lord critically appraised the health economic systematic review, critically appraised the economic

evaluation, and drafted the report, Jonathan Shepherd critically appraised the clinical effectiveness systematic review, drafted the report and is the project co-ordinator and guarantor.

Confidential (CON) information is highlighted in blue and underlined

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LIST OF ABBREVIATIONS

AE	Adverse event
AIC	Akaike information criteria
ALP + FUL	Alpelisib with fulvestrant
BIC	Bayesian information criteria
BNF	British National Formulary
CI	Confidence interval
CIC	Commercial in confidence
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
CQ	Clarification question
ctDNA	Circulating tumour DNA
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	External Assessment Group
ECOG	Eastern Cooperative Oncology Group
EMC	Electronic Medicines Compendium
EPAR	European Public Assessment Report
ER	Oestrogen receptor
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
EQ-VAS	EuroQol Visual Analogue Scale
ESMO	European Society for Medical Oncology
ESR1	Oestrogen receptor 1
ESR1-mut	ESR1 mutation
ET	Endocrine therapy
EVE + EXE	Everolimus with exemestane
GLH	Genomic Laboratory Hub
GnRH	Gonadotropin-releasing hormone
GMS	Genomic Medicine Service
HER2-	Human epidermal factor receptor 2-negative
HR+	Hormone receptor-positive

HR	Hazard Ratio
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient level data
IRC	Imaging review committee
ITT	Intent to treat
MAIC	Matching-adjusted indirect comparison
mBC	Metastatic breast cancer
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	Modified intent to treat
NGS	Next generation sequencing
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NR	Not reported
OS	Overall survival
PartSA	Partitioned survival analysis
PFS	Progression-free survival
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PIK3CA-mut	PIK3CA mutation
PRO	Patient-reported outcome
PRO-CTCAE	Patient-Reported Outcome Common Terminology Criteria for Adverse Events
PSA	Probabilistic sensitivity analysis
PSM	Parametric survival model
PSS	Personal Social Services
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RDI	Relative dose intensity
RR	Relative risk/risk ratio
SAE	Serious adverse event

SD	Standard deviation
SE	Standard error
SERD	Selective oestrogen receptor degrader
SLR	Systematic literature review
SmPC	Summary of product characteristics
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TSD	Technical Support Document
TTD	Time to treatment discontinuation
UK	United Kingdom
US	United States
VAS	Visual analogue scale
WTP	Willingness to pay

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Below we provide an overview of the key issues. Section 1.1 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.2 to 1.4 explain the key issues in more detail. Background information on the condition, health technology, evidence and information on the issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE). Overview of the EAG's key issues

Table 1 Overview of EAG key issues

ID	Summary of issue	Report sections
Issue 1	Uncertainty in the clinical effectiveness of elacestrant based on post-hoc trial sub-group analyses	3.2.4
Issue 2	Uncertainty in the results of the matched adjusted indirect comparison (MAIC)	3.3 and 3.4
Issue 3	Uncertain overall survival extrapolations for elacestrant and comparators	4.2.4.2.1 and 4.2.4.3.1
Issue 4	Lack of evidence on comparator treatment duration	4.2.4.2.3 and 4.2.4.3.3
Issue 5	Practical implications and cost of introducing ESR1 mutation testing in the NHS	4.2.6.5

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- Target population (subgroup 1): the overall survival (OS) extrapolation for elacestrant (gamma rather than log-logistic); the price of everolimus (from eMIT rather than BNF).

- Dual mutation subgroup (subgroup 2): the proportion of positive ESR1 mutation tests (20% rather than 50%).

1.1 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing overall survival
- Maintaining quality of life for longer due to extended progression-free survival

Overall, the technology is modelled to affect costs by:

- Increasing the cost of treatment in the target population (subgroup 1)
- Reducing the cost of treatment in the subgroup with a dual mutation (subgroup 2)
- Adding costs to introduce ESR1 testing

The modelling assumptions that have the greatest effect on the ICER are:

- The choice of OS extrapolations for elacestrant and the resulting difference in survival relative to comparators
- Differences in treatment duration for elacestrant (based on trial data) and comparators (assumed equal to PFS)
- Use of MAIC hazard ratios to model the comparator survival curves compared with independently fitted curves (using MAIC adjusted data for elacestrant)

1.2 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 1 Uncertainty in the clinical effectiveness of elacestrant based on post-hoc trial sub-group analyses

Report section	3.2.4
Description of issue and why the EAG has identified it as important	Elacestrant is indicated for the treatment of postmenopausal women, and men, with ER+/HER2- locally advanced or metastatic breast cancer with an activating ESR1-mutation who have disease progression following at

	least one line of endocrine therapy (ET) including a CDK4/6 inhibitor. The company proposes that treatment with elacestrant should be targeted at two sub-groups of people eligible according to the marketing authorisation: • Subgroup 1 is people with an ESR1-mutation who have disease progression following ≥*12 months prior treatment* with endocrine therapy in combination with CDK4/6 inhibitor. • Subgroup 2, nested within subgroup 1, comprises people with an ESR1-mutation *and a PIK3CA-mutation (dual mutation*) who have disease progression following ≥*12 months prior treatment* with endocrine therapy in combination with CDK4/6inhibitor. The clinical effectiveness evidence for elacestrant in these subgroups is based on post hoc analyses of patients from the ongoing pivotal phase III, multicentre, randomised, open-label, active controlled trial comparing the efficacy and safety of elacestrant to endocrine monotherapy treatment (the EMERALD trial). The EAG urges caution in the interpretation of these results due to: • Small sample sizes, notably for post hoc subgroup 2 (13% of randomised patients). • Some evidence of selection bias due to imbalances in baseline characteristics between trial arms, affecting post hoc subgroup 2. In this subgroup there was a higher percentage of patients in the elacestrant arm with certain adverse prognostic factors, suggesting slightly more advanced cancer than the comparator arm. The impact of these imbalances is unclear. • The trial was not statistically powered for subgroups, thus statistical significance cannot be inferred from the

	results. The findings should be considered as exploratory, hypothesis-generating, rather than confirmatory.
What alternative approach has the EAG suggested?	None at present
What is the expected effect on the cost-effectiveness estimates?	This is uncertain currently.
What additional evidence or analyses might help to resolve this key issue?	Ideally a follow-up RCT in which patients in subgroups 1 and 2 are randomised to elacestrant and SOC, based on an appropriate sample size calculation. However, it is not feasible to design and complete such a trial within the timeframe of this NICE technology appraisal.

Issue 2 Uncertainty in the results of the matched adjusted indirect comparison (MAIC)

Report section	3.3 and 3.4
Description of issue and why the EAG has identified it as important	None of the treatments in the standard of care comparator arm of the EMERALD trial match the company's chosen comparators in the decision problem. Furthermore, none of the trials of the company's chosen comparator treatments tested patients for the ESR1 mutation. This limited the ability to do an indirect treatment comparison of elacestrant in patients with the ESR1 mutation in the EMERALD trial versus comparator treatments in similar patients in comparator trials. Due to the scarcity of ESR1 mutation testing in the UK and Europe the company did a targeted search for sources of real-world evidence in the US. They selected a registry of patient health records (the Flatiron database) to obtain data on patients with the ESR1 mutation treated with the relevant comparators.

	The company constructed an unanchored matched adjusted indirect treatment comparison (MAIC) using individual patient data from patients treated with elacestrant in the EMERALD trial, matched to aggregate data from patients treated with everolimus and exemestane or alpelisib and fulvestrant in Flatiron. The EAG notes some uncertainties in the methods used to construct the MAIC: • A set of 14 prognostic factors/effect modifiers were identified by key opinion leaders, but little information is given on the process and methodology. Sufficient information was available for just 3 of the 14 factors to allow their inclusion in the MAIC for the purpose of matching patients from EMERALD to Flatiron. Some widely accepted prognostic factors were not included such as bone metastases; number of metastatic sites and de novo vs. recurrent/progressed disease. This is a key limitation of the MAIC. • Other limitations include small effective sample sizes after weighting, particularly for post hoc subgroup 2 (dual mutation), and imbalances in weighted prognostic factors between elacestrant and comparator, again, notably in post hoc subgroup 2. • It is not explicitly stated how data on duration of previous endocrine therapy was identified in Flatiron. Exposure time for previous CDK6/4 inhibitor treatment was available and the EAG assumes that exposure time for previous CDK6/4 inhibitor treatment = exposure time for previous endocrine therapy, since in practice CDK6/4 inhibitor is usually given in combination with endocrine therapy. • Limited detail is provided on the methods of searching for relevant sources of real-world evidence. The Flatiron database was selected based on a “targeted” search in the US, rather than a systematic global search.

What alternative approach has the EAG suggested?	The Flatiron database could be replaced in the MAIC with the alternative real-world evidence source considered by the company - Patient360 Breast (ConcertAI). This appears to have a smaller sample of relevant patients than Flatiron, but it may potentially provide more comprehensive data on prognostic factors. Though uncertainty would likely remain, it could nonetheless be informative for decision making (e.g. as a scenario analysis).
What is the expected effect on the cost-effectiveness estimates?	The impact on the ICER is uncertain
What additional evidence or analyses might help to resolve this key issue?	In the shorter term, additional real-world evidence with greater coverage of prognostic factors relevant to this patient population. If this is not available from Flatiron a systematic search might identify other relevant patient registries. In the longer-term, clinical trial data comparing elacestrant head-to-head with other available treatments (e.g. everolimus + exemestane or alpelisib + fulvestrant) in patients with ESR1 mutation and PIK3CA-mutations.

1.3 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 3 Uncertain overall survival extrapolations

Report section	4.2.4.2.1 and 4.2.4.3.1
Description of issue and why the EAG has identified it as important	There is high uncertainty over the OS extrapolations in the economic model due to the use of an unanchored MAIC, and the limited sample sizes for the subgroups from the EMERALD trial and the Flatiron comparator cohorts. We agree with the use of the gamma distribution for the everolimus + exemestane comparator in subgroup 1, as this is closest to current survival expectations. However, we consider that the company's choice of a log-logistic extrapolation for elacestrant that gives a long projected

	survival benefit is overly optimistic given the current evidence base. The company base case OS extrapolations for post hoc subgroup 2 are also uncertain, but do not give such an extended projection of survival benefit (survival estimates are similar between arms after 6 years).
What alternative approach has the EAG suggested?	For EAG analysis, we prefer a gamma OS extrapolation for elacestrant as well as for the comparator in subgroup 1. This gives a good statistical and visual fit in both arms and similar survival projections after 5 years.
What is the expected effect on the cost-effectiveness estimates?	The company's base case ICER increases from £24,893 to £43,793 pprer QALY gained in subgroup 1 (including the 1.2 QALY severity modifier weight) when a gamma distribution is used to extrapolate elacestrant OS (see 6.1.1.1).
What additional evidence or analyses might help to resolve this key issue?	Additional clinical expert opinion to assess the plausibility of the survival extrapolations. However, uncertainty over this issue cannot be resolved without more robust comparative evidence and longer follow-up.

Issue 4 Lack of evidence on comparator treatment duration

Report section	4.2.4.2.3 and 4.2.4.3.3
Description of issue and why the EAG has identified it as important	Mature data on treatment duration is available for elacestrant from the EMERALD trial. However, data on treatment duration is not available for comparators from the Flatiron cohorts. The company assume that time to treatment discontinuation (TTD) for the comparators is equal to PFS in the economic model. We are concerned about the potential for bias due to the use of different modelling assumptions for TTD in the elacestrant and comparator arms. This will result in over-estimation of treatment costs for the comparator relative to elacestrant if, in practice, a proportion of patients discontinue the comparator treatments before progression, as was observed for elacestrant. The difference between the

	company's TTD estimates for elacestrant and those for alpelisib + fulvestrant in subgroup 2 are particularly marked.
What alternative approach has the EAG suggested?	We report exploratory scenario analysis using an option included in the company's model to adjust the TTD curves for the comparators using an assumed hazard ratio relative to the comparator PFS.
What is the expected effect on the cost-effectiveness estimates?	The EAG scenario with ALP+FUL TTD estimated assuming a 0.5 hazard ratio relative to the ALP+FUL PFS curve in subgroup 2 changed the results of the company's base case from elacestrant being dominant to an ICER of £4,362 per QALY (see 6.1.1.2).
What additional evidence or analyses might help to resolve this key issue?	Additional evidence on the duration of treatment for alpelisib + fulvestrant in a population similar to subgroup 2 (dual mutation with at least 12 months of prior ET+CDK4/6i). Clinical expert opinion on expected treatment duration.

1.4 Other key issues: summary of the EAG's view

Issue 5 Introduction of ESR1 mutation testing

Report section	4.2.6.5
Description of issue and why the EAG has identified it as important	A test for ESR1 mutation would be necessary to assess patients' suitability for treatment with elacestrant, but this is not currently provided in the NHS. Genetic testing for breast cancer is routine prior to treatment, using a tissue sample and digital PCR assay. However, as ESR1 is an acquired mutation, analysis of the primary tumour sample may not be accurate. Digital PCR could be used to test for the ESR1 mutation when treatment with elacestrant is being considered. However, this would require a repeat biopsy, which may not reflect disease status due to tumour heterogeneity, and there is potential for delay to the start of treatment. In the EMERALD study, ESR1 testing was conducted using a blood sample and circulating tumour DNA (ctDNA) test. The company state that they would expect such a test to be

	introduced if elacestrant were to be recommended by NICE, as the PIK3CA test was introduced when alpelisib was recommended (TA816). North Thames NHS Genomic Laboratory Hub (GLH) currently provide a ctDNA test that can identify the ESR1 mutation (Marsden360 assay), and we understand that other NHS GLHs are exploring this or a similar approach. This test is relatively expensive and not routinely available. However, the cost would be likely to fall if testing for the ESR1 mutation and other potential treatment targets were to become routine, with next generation sequencing panel testing of ctDNA samples.
What alternative approach has the EAG suggested?	For their base case, the company assumed a cost of £300 per test (based on digital PCR) and 50% prevalence of ESR1 mutation: or £600 per case identified for treatment. We conducted exploratory scenario analysis assuming a higher cost for ctDNA ([redacted] or [redacted]) with and without adjustment for prevalence.
What is the expected effect on the cost-effectiveness estimates?	Assuming a cost of [redacted] per test and 50% prevalence ([redacted] per case identified), the company's base case ICER for subgroup 1 increases from £24,893 per QALY to £28,858 per QALY (QALY weight of 1.2 applied) The long-term impact on the ICER is lower if we assume that the cost of the ctDNA test would fall with routine use (e.g. £26,343 per QALY at [redacted] per test). It is also arguable that the test cost should not be adjusted for prevalence, or even that the test cost should not be included in ICER calculations, as and when NGS ctDNA testing were to become routine for multiple treatment targets at this point in the care pathway.
What additional evidence or analyses might help to resolve this key issue?	Further information on the expected cost of ESR1 mutation testing if implemented in the NHS.

1.5 Summary of EAG's preferred assumptions and resulting ICER

The cumulative effects of EAG preferred assumptions on the company's base case analysis are shown in Table 2 (subgroup 1 - *ESR1-mut* + ≥12 months prior ET with CDK4/6i population) and Table 3 (subgroup 2 - *ESR1-mut+PIK3CA-mut* + ≥12 months ET with CDK4/6i population). These results include a confidential patient access scheme (PAS) discount for elacestrant, but other drugs are costed at non-confidential NHS prices. We report results, including all confidential discounts for comparators and subsequent treatments in a confidential 'cPAS' addendum to this report.

Table 2 Cumulative effect of EAG changes to the company's base case analysis for subgroup 1 – patients with an activating ESR1-mutation with disease progression following ≥12 months prior treatment with ET + CDK4/6i

Scenario	Incremental cost	Incremental QALYs	ICER (£/QALY) No QALY weight	ICER (£/QALY) With 1.2 QALY weight
Company's base case	£18,883	0.632	£29,872	£24,893
+ Mean age from Flatiron ([redacted] years)	£18,872	0.630	£29,942	£24,952
+ Everolimus price from eMIT 2023	£30,080	0.630	£47,723	£39,769
+independent PSM extrapolation: Gamma for both arms	£27,898	0.317	£87,869	£73,224
EAG's base case	£27,898	0.317	£87,869	£73,224

Table 3 Cumulative effect of EAG changes to the company's base case analysis for *ESR1-mut+PIK3CA-mut* + ≥12 months ET with CDK4/6i population (subgroup 2)

Scenario	Incremental cost	Incremental QALYs	ICER (£/QALY)
Company's base case	-£12,269	0.277	Dominant
+ Mean age from Flatiron ([redacted] years)	-£12,269	0.277	Dominant
+ Proportion of positive cases after ESR1-mut testing (20%)	-£11,369	0.277	Dominant

Scenario	Incremental cost	Incremental QALYs	ICER (£/QALY)
EAG's preferred base case	-£11,369	0.277	Dominant

Modelling errors identified and corrected by the EAG are described in section 5.3. For further details of the exploratory and sensitivity analyses done by the EAG, see section 6.1.4.2.6.5

2 INTRODUCTION AND BACKGROUND

2.1.1 Introduction

This report is a critique of the company's submission (CS) to NICE from Menarini Stemline UK Ltd on the clinical effectiveness and cost effectiveness of elacestrant for treating oestrogen receptor-positive, HER2-negative advanced breast cancer with an ESR1-mutation after at least one endocrine treatment. It identifies the strengths and weakness of the CS. Clinical experts were consulted to advise the external assessment group (EAG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the EAG via NICE on 13th May 2024. A response from the company via NICE was received by the EAG on 4th June 2024 and this can be seen in the NICE committee papers for this appraisal.

2.2 Background

2.2.1 Background information on ER+/HER2- advanced breast cancer with an ESR1 mutation

The CS considers advanced / metastatic breast cancer to encompass people with unresectable (inoperable) Stage III locally advanced breast cancer and Stage IV metastatic breast cancer (mBC). Approximately 35% of people with early or locally advanced resectable breast cancer will progress to mBC within 10 years of diagnosis and approximately 13% of people with breast cancer will have advanced/mBC at diagnosis. Of the various histopathological subtypes of breast cancer (determined by oestrogen receptor (ER) and/or progesterone receptor (PR) and human epidermal factor receptor (HER2) status) the most common is ER+/HER2-, accounting for approximately 70% of cases. Survival rates at 5 years are 36%, reducing with each successive line of therapy.

The CS mentions that patients with ER+/HER2 breast cancer receiving endocrine therapy (ET) over time are at risk of acquired resistance, including acquired mutations in the ESR1 (Oestrogen receptor 1) gene, known as the ESR1 mutation or *ESR1-mut*. Acquisition of this mutation happens almost exclusively after treatment with an aromatase inhibitor (AI) and is more common with longer exposure to ET. It is stated that the prevalence of the ESR1-mutation is higher in those treated with an AI plus a CDK4/6 inhibitor compared to AI alone. The CS estimates that up to 50% of patients who have received an AI will develop the ESR1-mutation on disease progression, thus creating a "novel population" of ER+/HER2- ESR1-mutated advanced/metastatic breast cancer. Importantly, this population experiences faster disease progression and poorer survival than those without

an ESR1-mutation. The evidence cited in support of this claim comes from the company's analysis of studies of endocrine therapy in advanced hormone receptive breast cancer, including the BOLERO-2 trial,[1] the BYLieve trial,[2] Clatot et al (2016),[3] the MAINTAIN trial,[4] and pooled analysis of the SoFEA and EFFECT trials.[5]

Some patients with ER+/HER2- develop the PIK3CA mutation (Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) and some have both the PIK3CA mutation and the ESR1-mutation. The latter group are referred to in the CS as the "dual mutation" group and are eligible for elacestrant according to the marketing authorisation.

2.2.2 Background information on elacestrant

The CS describes elacestrant as a next-generation, nonsteroidal, orally bioavailable SERD (selective oestrogen receptor degrader). It received its marketing authorisation in the UK in December 2023 from the Medicines and Healthcare products Regulatory Agency (MHRA), and is indicated for *"the treatment of postmenopausal women, and men, with ER+/HER2-, locally advanced or mBC with an activating ESR1-mutation who have disease progression following at least one line of ET including a CDK4/6i."* (CS page 14, reproduced from the Summary of Product Characteristics).

Elacestrant is administered as an oral tablet (345 mg) once daily for as long as clinical benefit is observed or until unacceptable toxicity occurs. Dose modifications are permitted depending on adverse reactions, as detailed in the Summary of product characteristics (SmPC).

Elacestrant is described as the first targeted treatment option specifically indicated for patients with ER+/HER2- ESR1-mutated advanced/mBC. The CS states that patients with ER+/HER2- 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. However, the company notes that that genomic testing for the ESR1-mutation is not currently funded as standard practice in the UK. They anticipate that testing will be funded in the future with the introduction of elacestrant treatment. For the purposes of this NICE appraisal the company has included ESR1-mutation testing using liquid biopsy, based on polymerase chain reaction (PCR) testing (see section 4.2.6.5 of this report for a discussion of how testing is modelled in the economic evaluation).

Expert clinical advice to the EAG suggests that ESR1 testing is currently not widely available in the NHS, and that the introduction of testing would not likely introduce delays

to the clinical management of patients being considered for elacestrant therapy. Test turnaround times would likely be in-keeping with current commercial testing timelines. See section 4.2.6.5 for further discussion.

2.2.3 The current care pathway for advanced/metastatic ER+/HER2- breast cancer

The CS describes the current treatment pathway and where in the pathway the company suggests elacestrant would be of most benefit. They draw on recommendations from relevant clinical guidelines, notably the European Society for Medical Oncology (ESMO) Guideline for mBC and the ESMO mBC Living Guideline for patients with ER+/HER2- mBC. Recommendations from previous NICE appraisals of treatments for ER+/HER2- advanced/mBC are also mentioned, as well as NICE clinical guideline CG81 'Advanced breast cancer: diagnosis and treatment' and NG101 'Early and locally advanced breast cancer: diagnosis and management'.

2.2.3.1 First line therapy for advanced/metastatic breast cancer

Figure 1 reproduces the company's illustration of the treatment pathway (CS Figure 6) in the advanced/mBC setting. As can be seen, patients can receive successive lines of therapy as their cancer progresses. First line treatment is endocrine therapy (e.g. an aromatase inhibitor such as **anastrozole or letrozole**) combined with a CDK4/6 inhibitor (e.g. **palbociclib, ribociclib, abemaciclib**). Chemotherapy may be given if imminent organ failure is suspected.

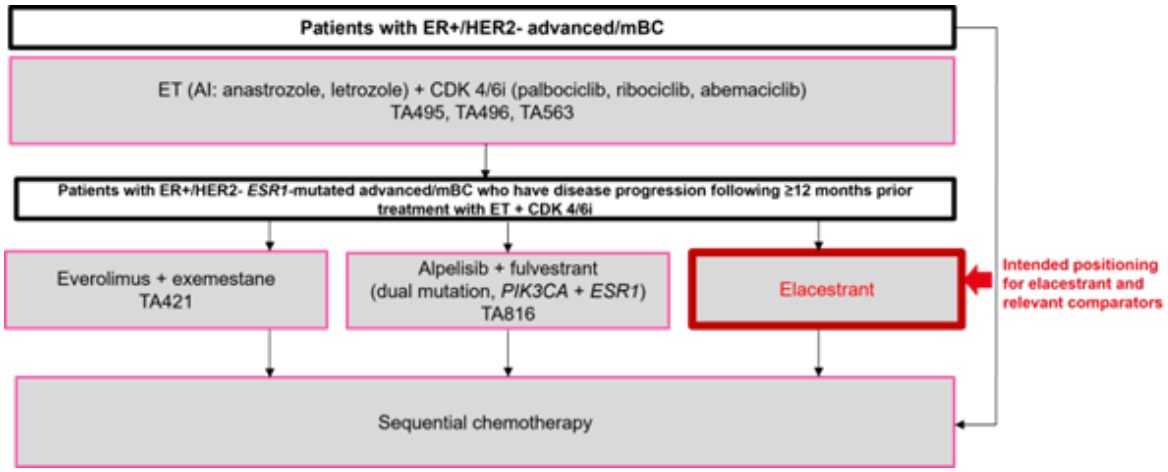

Figure 1 Current treatment pathway in England and Wales for patients with ER+/HER2- advanced/mBC

Source: Reproduced from CS Figure 6

The EAG notes that the pathway in Figure 1 doesn't distinguish between previously treated (adjuvant relapsed) patients and untreated patients with de novo advanced//metastatic disease.

Expert clinical advice to the EAG is that If relapse occurs whilst on an aromatase inhibitor, or less than 12 months after stopping, this is likely to indicate intrinsic resistance. Therefore, re-treatment with a drug sharing the same mechanism of action would be ineffective. Relapse more than 12 months after finishing treatment is more likely to be due to acquired resistance resulting in upregulation of the CDK pathways, which can be overcome by combining an aromatase inhibitor with a CDK4/6 inhibitor.

Patients with de novo advanced/metastatic breast cancer who have not been exposed to any previous hormonal therapy generally would be treated with a combination of an **aromatase inhibitor and a CDK4/6 inhibitor** (if premenopausal, they would also need to have ovarian suppression, usually with goserelin or a similar drug).

Our expert also commented that clinicians will soon start to see patients who are relapsing having already had a CDK4/6 inhibitor in the adjuvant setting. These patients would switch to an alternative hormone therapy (**aromatase inhibitor) or tamoxifen**. Some patients might also receive fulvestrant (depending on local funding agreements), or fulvestrant in combination with alpelisib (if PIK3CA mutated tumour, or exemestane + everolimus.

2.2.3.2 Second line therapy for advanced/metastatic breast cancer

Until elacestrant was licensed there were no available ESR1 mutation-targeted treatments and, hence, genomic testing for this mutation is not included in the current pathway. Instead, the CS states that advanced/metastatic breast cancer patients with an ESR1-mutation progressing from first line treatment are currently "managed empirically", with non-targeted medicines. It is unclear to the EAG what the company means by managed empirically, but we assume the choice of second line treatment is based on an assessment of signs, symptoms and prognostic factors (e.g. performance status) collectively indicating the aggressiveness of the tumour, the likely rate of progression and the fitness of the patient to undergo further treatment.

The CS identifies a subgroup of patients with ER+/HER2- ESR1-mutated advanced/ metastatic breast cancer who have disease progression following ≥12 months prior treatment with ET + CDK4/6i. This is the group the company propose should be offered elacestrant, as reflected in their decision problem and submission to NICE (see section 2.3 below for a discussion of the decision problem). The EAG notes that this is a narrower

population than that covered by the marketing authorisation - the latter does not stipulate a minimum duration of prior treatment with ET + CDK4/6i (≥12 months) before elacestrant can be given. We discuss the clinical rationale for this subgroup in section 2.3 below.

The EMSO metastatic breast cancer living guideline[6] for patients with ER+/HER2- metastatic breast cancer lists a number of treatment options for patients with ER+/HER2- advanced/metastatic breast cancer (CS Table 4). The guideline states that the optimal sequence of endocrine therapy after progression with an ET + CDK4/6i depends on factors such as which hormonal treatments the patient used previously, the duration of their response to prior treatment, tumour mutational status, disease burden and patient preference. Of the treatment options listed (excluding elacestrant itself which the EMSO guideline recommends for patients with an ESR1-mutation) the company considers two existing treatments as relevant for patients with ER+/HER2- ESR1-mutated advanced/ metastatic breast cancer who have disease progression following ≥12 months prior treatment with ET + CDK4/6i. These are:

- **everolimus and exemestane** (as recommended in NICE TA421) [7] and
- **alpelisib and fulvestrant** (as recommended for patients with the PIK3CA mutation in NICE TA816). [8]

As elacestrant is intended for use as a second line therapy these two dual therapies are relevant comparators for this appraisal (see section 2.3 for further detail on comparators).

The remaining second line treatments listed in the EMSO guideline are: **everolimus + fulvestrant** (preferred over everolimus + exemestane if the patient is ESR1-mutation positive); **switching ET ± CDK4/6i** or **fulvestrant monotherapy**; and **chemotherapy** for patients at imminent risk of organ failure. According to expert clinical opinion sought by the company, endocrine monotherapy, and endocrine therapy with chemotherapy, are rarely used in practice in the patient population under consideration in the CS (i.e. people with ER+/HER2- ESR1-mutated advanced/metastatic breast cancer who have disease progression following ≥12 months prior treatment with ET + CDK4/6i). The EAG's expert clinical adviser agrees.

The EAG notes that the CS does not comment on the EMSO guideline recommendation (CS Table 4) that **everolimus and fulvestrant** is preferred over **everolimus and exemestane** for treating ESR1 mutated tumours. However, expert clinical advice to the EAG is that everolimus and fulvestrant are not funded by the NHS.

Expert clinical advice to the EAG is that patients previously treated in the adjuvant setting who progress after first line treatment in the advanced/metastatic breast cancer setting would switch to

- A different aromatase inhibitor (usually from non-steroidal to steroidal) with or without everolimus,
- Or switch to tamoxifen.
- Or switch to fulvestrant + alpelisib if they have a PIK3CA mutated tumour (provided that they have not already received fulvestrant in combination with a CDK4/6 inhibitor).

Patients with de novo advanced/metastatic breast cancer who progress after first line treatment in the advanced/metastatic breast cancer setting would also switch to a different aromatase inhibitor or to tamoxifen. Patients with the PIK3CA mutation would switch to **alpelisib and fulvestrant** in combination. The expert commented that, contra to the EMSO guideline, fulvestrant monotherapy would not be used as it is not recommended by NICE (TA239).

2.2.3.3 Third line treatment for advanced/metastatic breast cancer

The CS does not comment on treatment options for patients who progress from second line treatment, other than noting that sequential chemotherapy is recommended by the EMSO guideline (CS Figure 4). The EAG's clinical expert advisor commented that factors taken into account when considering third line therapy include the patient's clinical condition, the extent of metastases, which sites are affected, the rate of disease progression and also their treatment history. Patients with hormone responsive cancer who progress on second line therapy might switch to third line hormone therapy, with whichever drugs they haven't already received. The expert also noted that many patients have slow progressing disease and are candidates for third line treatment.

2.2.4 Justification for the position of elacestrant in the treatment pathway

As described above, the company proposes elacestrant as a treatment for ER+/HER2- ESR1-mutated advanced/metastatic breast cancer who have disease progression following ≥12 months prior treatment with ET + CDK4/6i. The CS notes that since the introduction of ET+ CDK4/6i, there has been a rise in the prevalence of ESR1 mutations associated with prolonged duration of treatment. The CS notes that current standard treatments, such as the combination of everolimus and exemestane or alpelisib and fulvestrant, have not been evaluated in patients with ER+/HER2- ESR1-mutated advanced/metastatic breast cancer who have disease progression following ≥12 months of prior treatment with ET + CDK4/6i. Furthermore, the CS points out some of the limitations of current standard treatments,

citing significant toxicity (everolimus, alpelisib) and the pain and inconvenience of attending clinic to receive fulvestrant injections. The CS contends that there is increasing unmet need for a treatment specifically tailored for patients with the ESR1-mutation, with an acceptable safety profile and which can be taken orally rather than injected intramuscularly. This would be more convenient for patients and their carers and would require fewer healthcare resources to manage.

The EAG's expert clinical advisor commented that clinicians would view elacestrant as an oral drug that works in a similar way to fulvestrant, which has to be given by intramuscular injection. In the longer term it would be preferable for patients to have an oral alternative to fulvestrant. Fulvestrant is mostly used in combination with other drugs, however, there is currently no available evidence on the efficacy and safety of elacestrant in combination therapy.

EAG comment on the background information

The background section of the CS provides detailed information about the epidemiology of breast cancer, the course of disease and its subtypes, and the impact on morbidity and mortality. The anticipated place of elacestrant in the current treatment pathway is clearly defined, though the overall pathway depicted doesn't explicitly acknowledge that the choice of treatments for advanced/metastatic breast cancer will depend on the patient's previous treatment history, and may require switching to different hormone treatments at each successive line.

2.3 Critique of the company's decision problem

Table 4 summarises the NICE scope for this appraisal, the company's decision problem, and the EAG's critique of the company's approach. As the table shows, the decision problem adheres to the NICE scope, albeit with two notable exceptions: the patient population and the choice of comparator treatments.

Table 4 Summary of the decision problem

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
Population	People who have been through menopause and men with ER+/HER2- locally advanced or mBC with an activating ESR1-mut after at least 1 line of ET including a CDK4/6i.	Postmenopausal women, and men, with ER+/HER2-, locally advanced/mBC with an activating ESR1-mut who have disease progression following ≥12 months prior treatment with ET + CDK4/6i	This is the population of patients where clinicians perceive the most value for elacestrant to be in UK clinical practice. In a post hoc subgroup analysis of the pivotal phase III study (EMERALD), patients treated with elacestrant had a greater improvement in PFS with longer exposure (≥12 months) to prior ET +	The company clarified the rationale for ≥12 months of prior ET + CDK4/6i (as opposed to other potential thresholds for prior treatment). They presented a post-hoc subgroup analysis of the EMERALD trial at an international cancer conference in 2022.[9 10] Longer duration on CDK4/6i was associated with improvement in PFS for patients treated with elacestrant, and this was more pronounced in

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
			CDK4/6i vs. ET monotherapy. The results of this post hoc subgroup analysis support the beneficial activity of elacestrant in patients with longer exposure (i.e. ≥12 months) to prior ET + CDK4/6i.	patients with at least 12 months of prior CDK4/6i duration. The EAG notes that these subgroups (i.e. <6 months, 6-12 months, 12-18 months, ≥18 months) were selected post hoc after examination of the data. Whilst the results indicate greater PFS according to length of previous treatment, these findings are exploratory, and not confirmatory. The EAG also notes there is a similar pattern in the results of the All-patient population.
Intervention	Elacestrant	Elacestrant	Not applicable	No comment
Comparators	Everolimus + exemestane; ET with or without chemotherapy; the	Everolimus + exemestane;	UK clinical expert opinion suggests that:	Expert advice to the EAG confirms that endocrine

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
	Chemotherapy; Alpelisib + fulvestrant (for people whose BC is PIK3CA-mutated)	Alpelisib + fulvestrant (for people whose BC is PIK3CA-mutated)	ET monotherapy or ET + chemotherapy is rarely used in clinical practice in England and Wales in the patient population under consideration in this submission. Chemotherapy in the UK is reserved predominantly for patients with imminent risk of organ failure	monotherapy is not standard practice in the NHS.
Outcomes	OS PFS Response rate Adverse effects of treatment HRQoL	OS PFS Response rate Adverse effects of treatment HRQoL	Not applicable	No comment
Economic analysis	The reference case should be followed. The economic modelling should include the costs	Not stated	Not stated	The company do not refer to the economic analysis in the decision problem. However, as discussed in section 4.2.1 of this

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
	associated with diagnostic testing for ESR1 and where relevant, PIK3CA mutations in people with oestrogen receptor-positive HER2 negative locally advanced or metastatic breast cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.			report, the economic model complies with the reference case, and the cost of ESR1 testing is included in the model, (and removed in a sensitivity analysis).
Subgroups	Mutations in both ESR1 and PIK3CA	Mutations in both ESR1 and PIK3CA	For the dual mutated population only those patients progressing following ≥12 months prior treatment with ET + CDK4/6i are considered.	See comment above in Population

Source: Reproduced in part from CS Table 1

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

In CS Appendix D the company describe their systematic literature review (SLR) to identify clinical evidence (RCT and non-RCT) for elacestrant and comparators (everolimus + exemestane and alpelisib + fulvestrant) for ER+/HER2- ESR1-mutated advanced/metastatic breast cancer. The EAG 's appraisal of the company's systematic review methods is summarised in Appendix 1. Briefly, the company carried out an initial SLR, referred to in the CS as "the global clinical SLR", which had broader eligibility criteria for interventions and comparators than the NICE final scope (CS Appendix D Table 4). To identify relevant evidence for the appraisal, the company then used narrower eligibility criteria aligned with the NICE final scope (CS Appendix D Table 5), to rescreen included studies identified from the initial SLR. The EAG considers these narrower eligibility criteria appropriate in terms of the appraisal.

The EAG did, however, note two potential issues with the company's searches which may result in relevant evidence being missed. First, the searches were approximately eight months old when the CS was received by the EAG. Second, the RCT filter used in the searches excluded conference abstracts. The EAG therefore reran the company's searches for the last 8 months and, separately, the Embase search for the past three years using terms that would include conference abstracts. After deduplication, these EAG searches yielded a total of 217 records. The EAG screened all 217 titles and abstracts, and subsequent eight full papers, against the eligibility criteria aligned to the NICE final scope (CS Appendix D Table 5). None of these full papers were relevant to the NICE final scope. Overall, the EAG believe the company's review is comprehensive and matches the decision problem.

3.2 Critique of studies of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

The initial broader SLR identified 23 publications (CS Appendix D Figure 1). On rescreening these 23 publications against the narrower SLR eligibility criteria, which was aligned with the NICE final scope (CS Appendix D Table 5), 13 publications were subsequently excluded because the intervention was not relevant to the scope of this technology appraisal (CS Appendix D Figure 1). The company reports 10 publications were therefore relevant to the

NICE final scope (CS Appendix D.2, CS Appendix D Figure 1, CS Appendix D Table 6). Of these 10 publications:

- Seven publications concerned one RCT, the **EMERALD** trial, of the efficacy and safety of elacestrant versus clinician's choice of fulvestrant, anastrozole, letrozole, or exemestane monotherapy in postmenopausal women and men with ER+/HER2-, advanced or metastatic breast cancer, whose disease has relapsed or progressed on at least one and no more than two lines of prior ET for advanced or metastatic breast cancer, which must have included a CDK4/6i in combination with fulvestrant or an AI. A subgroup of these patients had an activating ESR1-mutation (ESR1-mut). Key results from the trial are presented in an article in the Journal of Clinical Oncology. [11]

- Three publications concerned two studies of alpelisib in combination with fulvestrant.
  - One non-RCT (BYLieve; NCT03056755; 2 publications)[2 12]
  - One retrospective real world cohort study (one publication)[13]
- The company reports that no evidence was identified for everolimus in combination with exemestane in the population defined in the company decision problem i.e. ESR1-mut and ≥12 months' prior ET including a CDK4/6i (CS section B.2.1).

CS section B.2.2 only lists the EMERALD RCT as the relevant clinical effectiveness evidence for the appraisal and CS document B section B.2.11 states that there are no other ongoing studies of elacestrant. At the EAG's request the company provided a detailed list of all elacestrant phase 1, phase 2 and phase 3 clinical trials (Company clarification response A3). After assessing this list, the EAG agree that the EMERALD trial is the only relevant trial of elacestrant for this appraisal.

3.2.1.1 Study characteristics

The **EMERALD** study (study RAD1901-308; ClinicalTrials.gov number NCT03778931)[11] is an ongoing phase III, multicentre, randomised, open-label, active controlled trial comparing the efficacy and safety of elacestrant to endocrine monotherapy treatment (investigator's choice of fulvestrant or an aromatase inhibitor) in postmenopausal women, or men, with ER-positive/HER2-negative advanced/metastatic breast cancer. The primary outcome of the trial was progression free survival (PFS) based on blinded imaging review committee (IRC)-assessment in either all patients (i.e. with ESR1 mutations (*ESR1-mut*) or without detectable ESR1 mutations *(ESR1-mut*-nd)) or in patients with ESR1 mutations only (CS B.2.3.1, B.2.11). Patients were enrolled from 17 countries, including the UK. Fifty four percent of patients were enrolled from Europe and 29.5% from North America. The trial results support

the company's regulatory marketing authorisation for elacestrant. Evidence from the trial also inform the assessments of cost-effectiveness in the company's economic model (CS B.2.2; see sections 4.2.4, 4.2.5.2 and 4.2.5.3 of this this report). The EAG note that the populations addressed in the company's submission, i.e. ESR1-mut only, or dual mutated (mutations in ESR1 and PIK3C), who have disease progression following ≥12 months prior treatment with ET + CDK4/6 inhibitors, are post-hoc specified subgroups (henceforth referred to in this report as "post-hoc subgroup 1 (ESR1 mutation)" and "post-hoc subgroup 2 (dual mutation)" respectively). Post-hoc subgroup 2 (dual mutation) itself is a subgroup nested within post-hoc subgroup 1 (ESR1 mutation). Table 5, below, summarises the EMERALD trial methodology.

Table 5 Summary of EMERALD trial methodology

Study characteristics	
Trial design	RCT Open label 2 arm - elacestrant versus standard of care (SOC) (investigator's choice of fulvestrant, anastrozole, letrozole, or exemestane monotherapy)
Randomisation	1:1 Stratified by ESR1-mut status (ESR1-mut vs. ESR1-mut not detected), prior treatment with fulvestrant (yes or no) or presence of visceral metastasis (yes or no) n=478 patients enrolled (including 12 from UK), of which 228 were ESR1-mut (including 9 from UK)
Evaluation of ESR1-mutational status	Evaluated in cell-free circulating DNA at a central laboratory; blood samples were analysed using the Guardant360 CDx (GuardantHealth, RedwoodCity, CA). ESR1 mutations defined as any missense mutation in codons 310 - 547. ESR1 mutation status was not provided to study sites during treatment.
Study duration	10/05/2019 – 08/2024 (estimated); no further data cuts expected. The company provided a CSR, along with its associated protocol, SAP and addendum. CSR v.2 reports trial results from a data cut of **06 September 2021** for the whole trial population and ESR1-mut population. This data cut includes the primary analysis of the primary outcome (blinded-IRC assessed PFS) and interim results

Study characteristics	
	of OS. The main findings of the trial, with the same data cut, were published in the Journal of Clinical Oncology (Bidard et al, 2022).[11] An overall survival addendum to CSR v.2, with a data cut of **02 September 2022**, reports the final OS analyses. For *post-hoc* subgroups [subgroups 1 and 2] the data cut was **02 September 2022** for PFS and OS, and **8th July 2022** for patient-reported outcome (PRO) data.
Location	Europe (Austria, Belgium, Denmark, France, Greece, Hungary, Ireland, Italy, Portugal, Spain, UK), Asia (Israel, South Korea), North America (Canada, United States), Other (Argentina, Australia).
Included population	Postmenopausal women, or men, aged ≥ 18 years with ER-positive/HER2-negative advanced or metastatic breast cancer who have progressed or relapsed following one to two prior lines of ET for advanced or metastatic disease, one of which was given in combination with a CDK4/6i. Patients must have received no more than one line of cytotoxic chemotherapy for metastatic breast cancer and had an ECOG PS of 0 or 1.
Excluded population	Patients with symptomatic metastatic visceral disease or any of the following cardiovascular events within 6 months of enrolment: severe/unstable angina, myocardial infarction, coronary/peripheral artery bypass graft, prolonged corrected QT interval grade ≥ 2, uncontrolled atrial fibrillation, ongoing grade ≥ 2 cardiac dysrhythmias, New York Heart Association Class II or greater heart failure, coagulopathy (thrombosis), cerebrovascular accident and in the UK patients were excluded if they had a QTcF of ≥450 msec.
***Post-hoc* specified subgroups of relevance to the submission**	**Post-hoc subgroup 1 (ESR1 mutation):** ESR1-mut who have received ≥12 months of prior ET + CDK4/6i **Post-hoc subgroup 2 (dual mutation):** Mutations in both ESR1 *and* PIK3CA (dual mutated) who have received ≥12 months of prior ET + CDK4/6i
Intervention	Elacestrant dihydrochloride 400 mg/day (equivalent to elacestrant 345 mg), once-daily orally. Protocol-defined dose reductions permitted to 300 mg or 200 mg daily.

Study characteristics	
Comparator	Investigator's choice of one of the following monotherapies [a]: **Fulvestrant:** 500 mg intramuscularly on cycle 1[b] day 1, cycle 1 day 15, cycle 2 day 1 and day 1 of every subsequent 28-day cycle **Anastrozole:** 1 mg/day orally on a continuous dosing schedule **Letrozole:** 2.5 mg/day orally on a continuous dosing schedule **Exemestane**: 25 mg/day orally on a continuous dosing schedule
Primary outcome	PFS based on blinded -IRC-assessment in i) all patients (i.e. with or without detectable ESR1 mutations) or ii) in patients with ESR1 mutations only.
Secondary outcomes informing the economic model	Overall survival, EQ-5D-5L, adverse events
Other secondary outcomes	**Efficacy:** Response rate (Blinded IRC assessed ORR, DOR and CBR) **HRQoL:** EQ-VAS score, EORTC QLQ-C30, PRO-CTCAE **Other:** time to chemotherapy **Safety:** treatment compliance and exposure, treatment emergent adverse events, deaths and serious adverse events.

Source: Partly reproduced from CS document B Table 6 and Table 7
Abbreviations: CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CSR, clinical study report; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D-5L, EuroQoL Five-dimension Five-level; ER, oestrogen receptor; ESR1, oestrogen receptor 1 gene; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HRQoL, health-related quality of life; IRC, imaging review committee; mut, mutation; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PIK3CA, phosphatidylinositol 3 kinase; PRO, patient-reported outcome; PRO-CTCAE, Patient-Reported Outcome Common Terminology Criteria for Adverse Events; RCT, Randomised Controlled Trial; RECIST, response evaluation criteria in solid tumours; SAP, statistical analysis plan; SOC, standard of care; UK, United Kingdom
[a] No other anti-cancer agents were allowed
[b] 28 day cycle
[c] Common Terminology Criteria for Adverse Events criteria

The EAG considers there are two issues regarding the design of the EMERALD trial in relation to this appraisal:

1. the choice of comparators and
2. the type of test used to assess ESR1 mutational status.

These are discussed in further detail below.

Comparators

As shown in Table 5 above, comparators used in the EMERALD trial were investigator's choice of one of the following monotherapies: fulvestrant, anastrozole, letrozole or exemestane. Clinical expert advice to the company were that the use of monotherapy after progression on CDK4/6i is not representative of standard clinical practice.[14] The EAG clinical expert agreed. Additional issues regarding comparators the EAG clinical expert highlighted were:

- Fulvestrant is not allowed to be used as a single agent in clinical practice due to NICE guidelines (TA239).[15]
- Some patients in the EMERALD trial comparator arm had prior exposure to a non-steroidal aromatase inhibitor and were assigned to receive another in the trial. Switching from one drug to another that works in the same way is rarely done in clinical practice as the likelihood of overcoming resistance would be expected to be very low. The company state that while patients in the EMERALD trial could also receive a steroidal aromatase inhibitor following a non-steroidal one and vice versa, this was not the preferred option. A few patients received several lines of therapy and may have received a similar AI in one of these prior lines, but not in the line directly prior to starting the trial.
- The lack of tamoxifen as a comparator choice is perplexing given that most patients in the EMERALD trial had no prior exposure to tamoxifen (approximately 8% in each arm of the ESR1-mut subgroup received tamoxifen as prior therapy; CS document B Table 9).

Test to evaluate ESR1-mutational status

The EAG clinical expert believed that the proposed test to identify ESR1-mutation status in the NHS is not the same, and has disadvantages, compared to the test used in the EMERALD trial.

The proposed test for the NHS would utilise a tissue sample, either a primary tumour sample, which is limited due to being a historic sample, or a single site repeat biopsy, which is limited by the potential to not fully reflect disease status due to within tumour heterogeneity. Conversely, the ESR-1 mutation status testing in the EMERALD trial is tissue free, using a current blood sample for circulating tumour DNA analysis (Emerald protocol section 7.6.2). It is therefore an assessment of the current tumour *and* is more likely to assess the totality of the tumour rather than that of an individual sample site.

3.2.1.2 Patients' baseline characteristics

The CS presents baseline characteristics for the following EMERALD trial populations only: all patients with ESR1-mut (CS B.2.3.1.2 and CS document B Table 9), and the post-hoc-subgroups 1 (ESR1 mutation) and 2 (dual mutation; CS B.2.7.1 and CS document B Table 20).

The CS states baseline characteristics for both post-hoc subgroups were similar to those of all patients with ESR1-mut (CS section B.2.7.1). Briefly, the median age of participants was approximately 63 years and all were female. In terms of race/ethnicity, most participants (approximately 75%) identified themselves as White. Approximately half of patients had ECOG performance 0 (indicating the participant is fully active with no performance restrictions) and the other half ECOG performance 1 (cannot do strenuous physical activity but is fully ambulatory and can do light work). The proportion of patients with visceral metastases (including lung, liver, brain, pleural, and peritoneal involvement) was approximately 75%. Over half of participants had received prior adjuvant therapy. In terms of prior treatment for advanced or metastatic disease, all participants had received prior CDK4/6i therapy and over 96% received prior ET with the remaining patients progressing during or within 12 months of adjuvant endocrine therapy. In the advanced or metastatic setting, approximately two-thirds of participants had one prior line of ET and one-third had two lines of prior endocrine therapy. In terms of experience with chemotherapy, approximately three-quarters of patients had no prior lines of chemotherapy and one-quarter had one-line of prior chemotherapy.

The CS states that baseline characteristics for all patients with ESR1-mut, and for both post-hoc subgroups, were well balanced between the two study arms (CS B.2.3.1.2, CS B.2.7.1). While the EAG in general agree with the company's statement, we note the following imbalances/differences with respect to the post-hoc subgroups (CS document B Table 20):

- Post-hoc subgroup 1 (ESR1 mutation):
  - A [redacted] proportion of the elacestrant arm received fulvestrant as prior therapy for advanced or metastatic disease compared to the SOC arm ([redacted])
  - A [redacted] proportion of the elacestrant arm received mammalian target of rapamycin (mTOR) inhibitor as prior therapy for advanced or metastatic disease compared to the SOC arm ([redacted])

- Post-hoc subgroup 2 (dual mutation):

- Median age was slightly [redacted] in the elacestrant arm than in the SOC arm ([redacted]).
- A [redacted] proportion of participants in the elacestrant arm has visceral metastasis (including lung, liver, brain, pleural, and peritoneal involvement) compared to the SOC arm ([redacted])
- A [redacted] proportion of the elacestrant arm received mTOR inhibitor as prior therapy for advanced or metastatic disease compared to the SOC arm ([redacted])
- In the advanced or metastatic setting a [redacted] proportion of the elacestrant arm received one prior line of endocrine therapy compared to the SOC arm ([redacted]), and a [redacted] proportion of the elacestrant arm received two prior lines of endocrine therapy compared to the SOC arm ([redacted]).

The above baseline characteristics indicate that patients in the elacestrant arm of post-hoc subgroup 2 (dual mutation) were [redacted] compared to patients in the SOC arm. The impact of these imbalances is unclear.

EAG comment on included studies

The EMERALD trial is a large ongoing phase III, multicentre, randomised, open-label, active controlled trial of the safety and efficacy of elacestrant. It was used as the source of evidence in the granting of the marketing authorisation and is the sole source of evidence on elacestrant to inform this NICE appraisal. The trial included a pre-specified subgroup of participants with the ESR1 mutation, comprising almost half of the randomised trial population (228/478 participants, 48%). One of the main limitations of the EMERALD trial is that the comparator arm (investigators choice of standard of care endocrine monotherapies), and therefore the elacestrant treatment comparison, is of limited relevance to the scope and the decision problem for this NICE appraisal.

3.2.2 Risk of bias assessment

The company's methodological quality assessment (also referred to as risk of bias assessment) of the EMERALD trial was conducted using the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in healthcare.[16] An overview of the company's assessment is presented in CS document B Table 12 and their full assessment, which includes justification for their judgements, is presented in CS Appendix D Table 7. The EAG independently critically appraised the trial using the same criteria, and an overview of

our judgements, alongside those of the company, are presented below in Table 6 (disagreements between the company and EAG judgements are in bold and are discussed the text below the table).

Table 6 Overview of company and EAG risk of bias judgements

Criterion	Company judgement	EAG judgement
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	No	Yes
Were the groups similar at the outset of the trial in terms of prognostic factors?	Yes	Yes
Were the care providers, patients and outcome assessors blind to treatment allocation?	No	No, with exception of blinded-IRC assessments, which includes primary analysis of PFS
Were there any unexpected imbalances in dropouts between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes for all outcomes except for missing data for EQ-5D-5L presented in the CS (Note, the economic model uses all the EQ-5D data collected, as per preferred NICE methodology)[a]

Source: Partly reproduced from CS document B Table 12 and CS Appendix D Table 7. Additional sources: CS B 2.3.1, CS document B figure 3, CS Appendix D figure 2, CSR sections 9.4.4 and 9.4.6, CSR Tables 14.1.4.1 and 14.1.5.1
Abbreviations: EQ-5D-5L, EuroQoL Five-dimension Five-level; IRC, imaging review committee; PFS, progression-free survival

[a] Company clarification response A5

The EAG agreed with the company's judgements for all criteria except the following:

Concealment of allocation

The company judged the concealment of allocation was inadequate due to the trial being open-label and therefore patients and investigators were not blind to treatment assignment. The EAG suggest that the company is confusing allocation concealment with blinding. Allocation concealment is performed when the treatment allocation system is set up so that the person enrolling participants does not know in advance which treatment the next person will get. CS Appendix D Table 7 and CSR section 9.4.4 describe randomisation being conducted by Interactive Randomization Technology (IRT), which provided the randomisation number and treatment assignment.[17] The EAG therefore consider that allocation concealment was adequate.

Blinding of care providers, patients and outcome assessors to treatment allocation

The company judged that as the trial was open-label, patients and investigators were not blind to treatment assignment. The EAG agree that patients and caregivers were not blind, therefore patient reported outcomes and safety-related outcomes could be subject to bias. However, response and progression, including the primary analysis of PFS included in the CS, were assessed by a blinded IRC. The risk of outcome assessment related bias for these outcomes is therefore unlikely. Furthermore, the key secondary outcome of overall survival was an objective outcome and therefore unlikely to be influenced by knowledge of the treatment received.

Missing data

There is considerable missing data for EQ-5D-5L index scores for the ESR1-mut subgroup (CS B.2.6.4). First, the company's decision to obtain EQ-5D-5L index scores only for countries in which the validated tool was available (5 out of 17 countries enrolled in the trial; see company clarification response A5) resulted in large differences in the number of patients in each arm of the ESR1-mut subgroup with an EQ-5D-5L index score versus an EQ-VAS score (50 (43%) versus 108 (94%) in the elacestrant arm and 50 (44%) versus 98 (87%) in the SOC arm). The company clarified that this issue is in relation to EQ-5D-5L index scores presented in the CS but that the economic model uses all the EQ-5D data collected.

Second, there is a difference in the total number of patients with ESR1-mut enrolled in [redacted]; CSR Table 14.1.1.2) of the [redacted] countries and those that had a baseline EQ-5D-5L score (CSR Table 14.2.6.4.1). In total [redacted] ESR1-mut patients were enrolled from these [redacted] countries, with [redacted] assigned to elacestrant and [redacted] to SOC, yet baseline EQ-5D-5L index scores are only available for [redacted] patients in each arm (CSR Table 14.1.1.2 and CSR Table 14.2.6.4.1). It is unclear to the EAG why there is this discrepancy.

3.2.3 Outcomes assessment

All outcomes included in the NICE scope (OS, PFS, response rate, adverse effects of treatment and HRQoL) were measured in the EMERALD trial.[18] CS document B, CS Appendix E, and company clarification response A9 present results of these outcomes for all patients with ESR1-mut, and for the two post-hoc subgroups. Results for the whole EMERALD trial population i.e. with or without ESR1-mut, were reported in the main trial publication (Bidard et al., 2022) [11] and in the CSR provided by the company.[11 17] Table 7 provides a summary of the NICE scope and decision problem related outcomes reported in the EMERALD trial.

Table 7 List of NICE scope and decision problem related outcomes reported in the EMERALD trial

Endpoint	Outcome	Definition
Primary	Blinded IRC-assessed progression free survival (PFS)	Length of time from randomisation until the date of objective disease progression per RECIST version 1.1 or death from any cause
Key secondary	Overall survival (OS)	Length of time from randomisation until the date of death from any cause
Other secondary	Blinded IRC-assessed objective response rate (ORR)	Percentage of patients with measurable disease who had achieved either a confirmed CR or PR per RECIST v1.1
	Blinded IRC-assessed clinical benefit rate (CBR)	Percentage of patients who had achieved either a confirmed CR or PR or stable disease at ≥24

Endpoint	Outcome	Definition
		weeks from randomisation per RECIST v 1.1
	Blinded IRC-assessed duration of response (DOR)	Duration of time from the date when criteria are met for either a CR or PR (whichever is first recorded) per RECIST v1.1 until the first date that recurrent or PD is objectively documented, or death from any cause
	Safety and tolerability	AEs: deemed treatment related if they occurred after the first dose of study drug and ≤30 days after the last dose of study drug SAEs led to death, hospitalisation, or prolonged hospitalisation, persistent or significant incapacity or disruption to normal daily life, congenital anomaly/birth defect, were life-threatening or required intervention to avoid one of the above Dose modifications Clinical laboratory parameters, ECGs, ECOG performance status, and vital signs
	Patient reported outcomes (PROs) and health related quality of life (HRQoL)	EQ-5D-5L, EORTC QLQ-C30 and PRO-CTCAE

Source: Partly reproduced from CS document B Table 8
AE, adverse event; CBR, clinical benefit rate; CR, complete response; DOR, duration of response; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EOT, end of treatment; EQ-5D-5L, EuroQoL Five-dimension Five-level; HRQoL, health-related quality of life; IRC, imaging review committee; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PRO, patient-reported outcomes; PRO-CTCAE, Patient-Reported Outcome Common Terminology Criteria for Adverse Events; RECIST, response evaluation criteria in solid tumours; SAE, serious adverse event

For the whole ESR1-mut population, the CS reports the final OS from a data cut of 02 September 2022 and for the remaining efficacy and safety results from a data cut of 06 September 2021. For both post-hoc subgroups the data cut off was 02 September 2022 for PFS and OS and response rates, and 8th July 2022 for patient-reported outcomes (PRO) and adverse events data.

Outcomes informing the economic model were:

- Progression free survival (for post-hoc subgroups 1 (ESR1 mutation) and 2 (dual mutation); CS B.3.3.4)
- Overall survival (for post-hoc subgroups 1 (ESR1 mutation) and 2 (dual mutation); CS B.3.3.4)
- Time to treatment discontinuation
- HRQoL via the EQ-5D-5L (for subgroup 1 (ESR1 mutation) mapped to the EQ-5D-3L). Company clarification response A5 stated that the overall EQ-5D scores reported in clinical sections of the CS (B.2) are based on a subset of the EQ-5D data collected in EMERALD, but the economic model uses all the EQ-5D data collected, as per preferred NICE methodology. The EAG discuss this further in section 3.2.2*,* and in the cost-effectiveness section 4.2.5.2 below*.*
- Adverse events for elacestrant (Grade ≥ 3 occurring in ≥2% of patients receiving elacestrant in the ESR1-mut subgroup; CS B.3.4.4)

Appendix 2 of the trial protocol and CSR Table 6 show the methods, frequency and timing of all outcome assessments were identical between trial arms, reducing the risk of evaluation time bias.[17 19]

EAG comment on outcomes assessment

Overall, we consider the efficacy, HRQoL and safety outcomes to be appropriate to the decision problem and scope.

3.2.4 Statistical methods of the included studies

The CS provided details of the statistical methods used in the EMERALD trial in the CS, with additional detail to be found in the study protocol, SAP, CSR, and in company clarification response A5. A summary and EAG critique of the statistical methods used in the EMERALD trial are presented below in Table 8.

Table 8 Summary and critique of the statistical methods used in the EMERALD trial

Analysis populations
Intention-to treat (ITT) population: defined as all randomised subjects, with patients analysed according to their randomized treatment assignments. This is the primary analysis population for **PFS, OS** and **PROs**, including **HRQoL** (All ITT patients: N=478; ESR1-mut N=228) Per protocol (PP) and modified per protocol (mPP): defined as all randomised patients except those who had a major protocol deviation. This population was used for **sensitivity analyses for PFS** if the primary endpoint was statistically significant. (All PP patients: N=464; ESR1-mut PP: N=221; all mPP patients: N=461; ESR1-mut N=219) Response Evaluable (RE) population: defined as 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 non-target) lesions and/or had a new lesion. This is the analysis population for **ORR** and **DoR.** (IRC assessed RE population: All patients: N=361; ESR1-mut N=171) Clinical Benefit Evaluable (CBE) population: defined as all ITT subjects who had measurable and/or evaluable disease (i.e. target and/or non-target lesions) at baseline and at least 1 post-baseline RECIST assessment on any (target or non-target) lesions and/or had a new lesion. This is the analysis population for **CBR.** (IRC assessed CBE population: All CBE patients: N=443; ESR1-mut N=212) Safety population: defined as all patients who received at least 1 dose of study medication. Patients were analysed according to the treatments they actually received in Cycle 1 [CSR section 9.7.1.2 p64]. This is the analysis population for **all safety outcomes** (All safety patients: N=467; ESR1-mut N=221)
EAG comment: The analysis populations are appropriate. As a proportion of all randomised patients, the safety population included 97.7% and the ESR1-mut safety population subgroup included 96.9%, thus minimal attrition bias.
Sample size calculations
The power calculation was based on the primary outcome, PFS. It was planned that 200 patients with ESR1-mut would need to be randomised to obtain **160** PFS events to provide 80% power to detect an HR of 0.610 at the two-sided alpha level of 2.5%. (CS Table 11). For all patients (ESR1-mut and ESR1-mut not detectable), 466 patients would

need to be randomised to obtain approximately **340** PFS events to have 92% power to detect a HR of 0.667 at the 2-sided alpha level of 2.5% (SAP 4.1)

EAG comment: CS B.2.12.2.1 states the final PFS analysis was conducted after **140** events due to an additional year needed to observe the pre-specified 160 number of events for the ESR1-mut subgroup. There were **300** events for the whole EMERALD trial population at this timepoint (CSR section 11.6.2.11). The EAG therefore considers the study to have reduced power and therefore uncertainty in the results of PFS for all patients and for the ESR1-mut subgroup.

Methods to account for multiplicity

The truncated Hochberg procedure was used to adjust for multiple statistical testing of the primary endpoints PFS for all patients and for patients with ESR1-mut only, and OS for all patients and for patients with ESR1-mut only (CS document B Table 11, CSR section 9.6.2)

EAG comment: The company's approach to handling multiple testing of outcomes is appropriate.

Analysis of outcomes

Primary analysis

Blind-IRC assessed PFS was performed on the ITT population incorporating randomisation stratification factors (for all patients these include ESR1- mutational status (ESR1-mut vs ESR1-mut-nd), prior treatment with fulvestrant (yes vs no), and presence of visceral metastases (yes vs no); for ESR1-mut subjects only, this includes prior treatment with fulvestrant (yes vs no) and presence of visceral metastases (yes vs no)). The Kaplan-Meier (KM) method was used to summarise time-to event outcomes. The Cox-proportional hazards model was used to estimate hazard ratios with 95% CI. The difference between treatment groups was analysed using the stratified log-rank test with the randomisation stratification factors for generation of p-value.

Key secondary outcome

OS was analysed using the same methods for PFS. (SAP 4.7.1, 4.7.2.1, 4.7.3.3). An interim OS analysis was performed at the primary PFS analysis, with a pre-specified adjusted 2-sided alpha level of 0.0001. The final analysis of OS was performed after the pre-specified 50% of patients had died, with a 2-sided alpha level of 0.0499 (SAP 4.7.2.1)

Secondary outcomes

ORR was compared between treatment groups using the Cochran-Mantel-Haenszel tests adjusting for randomisation stratification factors. The same methods were used for **CR**.

DoR was analysed using the KM method.

For **PROs** (**EQ-5D-5L**, **EORTC QLQ-C30** and the **PRO-CTCAE**) changes from baseline by study visit (with 95% CI) for each treatment group were used. In addition, for EORTC QLQ-C30, mixed model repeated measures (MMRM) were used to analyse change from baseline over study visits through to cycle 6.

For **safety outcomes,** only descriptive statistics (e.g., frequency, counts) were used.

EAG comment: Appropriate analytical methods were used for primary and secondary outcomes.

Handling of missing data

PFS (Primary analysis)

Censoring rules for the primary analysis of blinded IRC assessed PFS in the CS (CS document B Table 8) specified date of progression or censoring relating to missing assessments in the primary analysis:

- No baseline measurable or evaluable lesion: from date of randomisation
- No post-baseline assessments and no death: from date of randomisation
- Censored progression or death after missing ≥2 consecutive post-baseline tumour assessments: on date of last tumour assessment before missed assessments or date of randomisation, whichever is later.

The SAP (Table 2) additionally specified the date of progression for documented progression or death after missing 1 post-baseline tumour assessment should be the date of documented progression or death.

EQ-5D-5L

The company only had EQ-5D-5L index scores for countries in which the validated tool was available (5 countries: Denmark, France, Spain, UK and USA). For all other patients in the other countries the overall score was set to missing (Company clarification response A5). This missing data issue is in relation to EQ-5D-5L index scores presented in the clinical effectiveness section of the CS (B.2 and Appendix E) only - it does not apply to the EQ-5D analysis used to inform the economic model (CS B.3.4.1 and B.3.4.2, and clarification response B4 and Table 6).

EAG comment:

Primary analysis

Censoring relating to missing assessments in the primary analysis for PFS was similar between treatment groups for both ESR1-mut group and for all patients (CSR section .4.1.1).

EQ-5D-5L
The company's decision to obtain EQ-5D-5L index scores only for countries in which the validated tool was available (5 out of 17 countries enrolled in the trial) resulted in large differences in the number of patients in each arm of the ESR1-mut subgroup with an EQ-5D-5L index score versus an EQ-VAS score (50 (43%) versus 108 (94%) in the elacestrant arm and 50 (44%) versus 98 (87%) in the SOC arm). EQ-5D-5L index score data for the ESR1-mut subgroup presented in the clinical effectiveness section CS B.2 and for post-hoc subgroups 1 (ESR1 mutation) and 2 (dual mutation) in CS Appendix E should be interpreted with due caution given this small, unrepresentative sample.

Sensitivity analyses

PFS
For events that were recorded after missing 2 or more consecutive tumour assessments: '**actual event PFS analysis**' that defined the event date as the actual event date after the 2 missed tumour assessments.

For events that were recorded after missing 2 or more consecutive tumour assessments a '**backdating PFS analysis**' which defined the event date as the date of the next scheduled tumour assessment after the last adequate tumour assessment.

Assessing the impact of stratification and compared the two treatment groups using an **unstratified log-rank test**.

Using **Per Protocol population** in the same manner as the primary efficacy analysis if the primary endpoints were statistically significant.

Patient reported outcomes (PROs)
Excluding patients who had **at least 1 missing visit due to COVID-19**. Performed for all PRO outcomes in the same manner as the primary PRO analyses.

EAG comment: The sensitivity analyses are comprehensive.

Subgroup and post-hoc analyses

Pre-specified subgroup analyses (in addition to ESR1-mut) included:

- Prior treatment with fulvestrant; presence of visceral metastasis; age (<65 years, ≥65 years, <75 years. ≥75 years); race (Caucasian, Asian, other); region (Europe, North America, Asia); baseline ECOG Performance Status (0,1); measurable disease at baseline (yes, no); number of prior lines of endocrine therapy in the advanced/metastatic setting (1,2); number of lines of chemotherapy in the advanced/metastatic setting (0,1).

These subgroup analyses were performed for PFS, OS, ORR, DoR and CBR outcomes. CS document B section 2.7 specified that subgroup analyses were not performed if the number of patients in the subgroup of each treatment group was <5% however, company clarification response A6 confirmed these analyses were performed regardless of this threshold.

Post-hoc subgroup analyses reported in the CS included patients with:

- ESR1-mut who had received ≥12 months of prior ET + CDK4/6i (referred to as "post-hoc subgroup 1 (ESR1-mutation)" in this report), and
- ESR1-mut and PIK3CA mutations (dual mutated) who had received ≥12 months of prior ET + CDK4/6i (referred to as "post-hoc subgroup 2 (dual mutation)" in this report).

Company clarification response A7 provides a list of post-hoc analyses from the EMERALD trial in the public domain as conference abstracts.

EAG comment:

- The chosen pre-specified subgroups are appropriate to this condition. However, clinical expert advice to the EAG is that bone metastases is a very important prognostic factor and should have considered for inclusion as a subgroup.
- The CS presents results of pre-specified subgroup analyses only for blinded IRC-assessed PFS (as opposed to other outcomes), and for the ESR1-mut population (not the whole trial population) (CS Appendix E.1).
- As the CS itself notes, the trial was not statistically powered for subgroups, therefore statistical significance cannot be inferred from the results of any subgroup analyses.

Additional caution is needed in the interpretation of the two post hoc subgroup analyses:

- The sample sizes are small, notably in subgroup 2 (dual mutation group). Subgroup 1 included 33% of the randomised trial population (n=159/478); Subgroup 2 included 13% of the randomised trial population (n=62/478).

- In subgroup 2, the distribution of patients between the elacestrant and SOC trial arms is slightly uneven (11% vs 15%, respectively).
- Baseline characteristics (demographic, treatment history and performance status) were generally balanced across the trial arms, but with some notable differences in the percentage of patients in each arm (10% to 20% of patients) mainly affecting subgroup 2 (dual mutation patients). In this subgroup there was a [redacted] percentage of patients in the elacestrant arm with visceral metastases. Likewise, a [redacted] proportion of elacestrant patients previously had two lines of endocrine therapy in the advanced/metastatic setting, and [redacted] had received prior adjuvant therapy. This suggests that patients treated with elacestrant were in a [redacted] than was the case for patients receiving standard of care endocrine monotherapy.
- The post hoc status of the subgroup analysis means the results are at increased risk of bias, although the impact of these imbalances is unclear.Post hoc subgroup analyses in clinical trials should be considered as exploratory, hypothesis generating, rather than being confirmatory.

The list of post-hoc analyses provided by the company is limited to those in the public domain. It is unclear whether additional post-hoc analyses were performed that are not in the public domain.

Source: Partly reproduced from CS Table 11. Additional sources: CS B. 2.12.2.1; CS document B Table 10, CS Appendix E.1; Protocol section 11.2; SAP sections 3.1, 4.1, 4.7.1, 4.7.2.1, 4.7.3.3 and 4.8.4; CSR sections 4.1.1, 9.6.2, 9.7.1.2, 11.4.1.1 and 11.6.2.11; CSR Tables 11, 14.2.1.1.1 and 14.2.1.1.2; Company clarification response A5
Abbreviations: CBR, clinical benefit rate; CR, complete response; DOR, duration of response; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D-5L, EuroQoL Five-dimension Five-level; ESR1, oestrogen receptor 1 gene; HRQoL, health-related quality of life; IRC, imaging review committee; mut, mutation; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PRO, patient-reported outcomes; PRO-CTCAE, Patient-Reported Outcome Common Terminology Criteria for Adverse Events; SOC, standard of care.

EAG comment on study statistical methods

The main limitation of the statistical analysis of the EMERALD trial was that the study was not adequately powered for the analysis of the primary efficacy outcome (PFS) for all patients and for the ESR1-mut subgroup. The EAG therefore considers there is uncertainty in the results of PFS for all patients and for the ESR1-mut subgroup. Furthermore, results for the two post-hoc subgroups, 1 (ESR1 mutation) and 2 (dual mutation) should also be interpreted with caution given they were not powered to detect statistical significance, are relatively small in sample size and were selected for analysis

based on knowledge of their results, rather than being pre-specified before data collection.

3.2.5 Efficacy results of the intervention studies

Below we summarise results from the EMERALD trial for outcomes used in the economic model, namely progression free survival, overall survival, HRQoL via the EQ-5D-5L, and adverse events. Results for other outcomes (e.g. tumour response) are available in the CS and/or the trial CSR.[17]

3.2.5.1 Progression-free survival (PFS)

Blinded-IRC assessed PFS was the primary endpoint of the EMERALD trial. The company submission reported results for blinded-IRC assessed PFS for the ESR1- mut subgroup (CS document B section 2.6.1), post-hoc subgroup 1 (ESR1-mutation; CS document B section 2.7.2.1) and post-hoc subgroup 2 (dual mutation; CS document B section 2.7.3.1). Results for blinded-IRC assessed PFS for all patients were reported in Bidard et al., 2022 and the CSR.[11 17]

ESR1-mut subgroup

Table 9 summarises the primary analysis of blinded IRC-assessed PFS for the ESR1-mut subgroup in the ITT population. At the 6 September 2021 data cut a total of 140 PFS events had been recorded which was less than the 160 PFS events planned for the primary analysis (see Table 8). The EAG therefore considers the study to have reduced power and therefore uncertainty in the results of PFS for the ESR1 mut subgroup presented.

Fewer patients in the elacestrant arm progressed or died compared to the SOC arm (n=62 [53.9%] vs. 78 [69.0%], a difference of 15.1%). An absolute increase of 1.9 months in median PFS was observed with elacestrant (3.8 months; 95% CI 2.17 to 7.26) versus SOC (1.9 months (95% CI 1.87 to 2.14). The stratified HR was 0.55 (95% CI 0.39 to 0.77) signifying a 45% reduction in the risk of disease progression or death in patients with the ESR1 mutation receiving elacestrant.

Table 9 Primary analysis of blinded IRC-assessed PFS in the ESR1-mut subgroup in the EMERALD trial

	Elacestrant **N=115**	**SOC** **N=113**
HR (95% CI) P-value	0.55 (0.39 to 0.77) 0.0005	

	Elacestrant N=115	SOC N=113
Median PFS months (95% CI)	3.8 (2.17 to 7.26)	1.9 (1.87 to 2.14)
Events, n (%) Death Progression	62 (53.9) 3 (2.6) 59 (51.3)	78 (69.0) 1 (0.9) 77 (68.1)
3-month PFS rate (95% CI)	55.93 % (45.80 to 66.05)	39.55% (29.44 to 49.65)
6-month PFS rate (95% CI)	40.8% (30.1 to 51.4)	19.1% (10.5 to 27.8)
12-month PFS rate (95% CI)	26.8% (16.2 to 37.4)	8.2% (1.3 to 15.1)
18-month PFS rate (95% CI)	24.33% (13.68 to 34.98)	-

Source: Reproduced from CS Table 13
Abbreviations: CI, confidence interval; ESR1, oestrogen receptor 1 gene; HR, hazard ratio; IRC, imaging review committee; mut, mutation; PFS, progression-free survival; SOC, standard of care

The Kaplan Meier plot of blinded IRC assessment of PFS (CS figure 9, not reproduced here) shows a separation of the survival curves after 2 months. A consistently higher proportion of patients remained alive and progression free in the elacestrant arms compared to SOC at 2 months, 6 month, 12 months and 18 months.

Sensitivity analyses were consistent with results of the primary study in the ITT population (see Table 10). Results for pre-specified subgroup analyses are reported in section 3.2.5.4.

Table 10 Sensitivity analyses of blinded IRC-assessed PFS in the ESR1-mut subgroup in the EMERALD trial

Sensitivity analysis[a]	Hazard ratio	95% CI	P-value
Actual event PFS	0.542	0.385 to 0.759	0.0004
Back dating PFS	0.542	0.385 to 0.759	0.0004
Unstratified	0.531	0.378 to 0.743	0.0002
Per protocol population	0.543	0.385 to 0.764	0.0005

Source: Partly reproduced from CSR Tables 14.2.1.2.1, 14.2.1.3.1, 14.2.1.4.1 and 14.2.1.6.1
Abbreviations: CI, confidence interval; ESR1, oestrogen receptor 1 gene; IRC, imaging review committee; mut, mutation; PFS, progression-free survival
[a] See Table 8 of this report for definitions of these sensitivity analyses

All patients

Overall, the results for blinded IRC-assessed PFS for all patients were consistent with those for the ESR1-mut subgroup, albeit the reduction in the risk of disease progression or death with elacestrant compared to SOC was less (30%; HR 0.70; 95% CI 0.55 to 0.88; Bidard et

al., 2022; CSR Tables 17, 14.2.1.2.2, 14.2.1.3.2, 14.2.1.4.2 and 14.2.1.6.2).[11 17]. It should be noted that at the 6 September 2021 data cut a total of 300 PFS events had been recorded which was less than the 340 PFS events planned for the primary analysis (see Table 8). The EAG therefore considers the study to have reduced power and therefore uncertainty in the results of PFS for all patients.

Post-hoc subgroups 1 (ESR1 mutation and ≥12 months prior ET + CDK4/6i) and 2 (dual mutation)

Table 11 summarises analyses of blinded IRC-assessed PFS, with a data cut of 2 September 2022, for post-hoc subgroups 1 (ESR1 mutation) and 2 (dual mutation). Interpretation of the following results of these post-hoc analyses should be made with caution given they were not powered to detect statistical significance.

Table 11 Blinded IRC-assessed PFS in post-hoc subgroups 1 (ESR1 mutation) and 2 (dual mutation) in the EMERALD trial

	Post-hoc subgroup 1 (ESR1 mutation)		**Post-hoc subgroup 2 (dual mutation)**	
	Elacestrant N=78	SOC N=81	Elacestrant N=27	SOC N=35
HR (95% CI) p-value	0.410 (0.262 to 0.634) <0.0001		0.423 (0.176 to 0.941) -	
Median PFS months (95% CI)	8.61 (4.14 to 10.84)	1.91 (1.87 to 3.68)	5.45 (2.14 to 10.84)	1.94 (1.84 to 3.94)
Events, n (%) Death Progression	39 (50) 1 (1.3) 38 (48.7)	53 (65.4) 1 (1.2) 52 (64.2)	[redacted]	[redacted]
3-month PFS rate (95% CI)	68.30 (56.67 to 79.93)	41.55 (29.19 to 53.90)	[redacted]	[redacted]
6-month PFS rate (95% CI)	55.81 (42.69 to 68.94)	22.66 (11.63 to 33.69)	[redacted]	[redacted]
12-month PFS rate (95% CI)	35.81 (21.84 to 49.78)	8.39 (0.00 to 17.66)	[redacted]	[redacted]
18-month PFS rate (95% CI)	28.49 (14.08 to 42.89)	0.00 (-)	[redacted]	[redacted]

Source: Reproduced from CS Tables 21 and 23
Abbreviations: CI, confidence interval; ESR1, oestrogen receptor 1 gene; HR, hazard ratio; IRC, imaging review committee; n, number of patients with the observed characteristic; N, total number in group; PFS, progression-free survival; SOC, standard of care

Overall, the results for both post-hoc subgroups 1 (ESR1 mutation) and 2 (dual mutation) were consistent to those for the ESR1-mut subgroup, albeit:

- The reduction in the risk of disease progression or death with elacestrant compared to SOC was greater (post-hoc subgroup 1 (ESR1 mutation): 59%; HR 0.41 95% CI 0.26 to 0.63; post-hoc subgroup 2 (dual mutation): 58%; HR 0.42 95% CI 0.18 to 0.94; ESR1-mut: 45%; HR 0.55 (95% CI 0.39 to 0.77).
- The absolute increase in median PFS observed with elacestrant versus SOC was greater (post-hoc subgroup 1 (ESR1 mutation): 6.7 months; post-hoc subgroup 2 (dual mutation): 3.51 months; ESR1-mut: 1.9 months).

Clinical expert advice to the EAG were that the absolute median increase in PFS observed with elacestrant versus SOC in post-hoc subgroup 1 (ESR1-mut) would provide a meaningful benefit to most patients, while that observed in post-hoc subgroup (dual mutation) was less so.

As with ESR1-mut subgroup, Kaplan Meier plots for post-hoc subgroups 1 (ESR1 mutation) and 2 (dual mutation) (CS Figures 12 and 14 respectively; not reproduced here) show a separation of the survival curves after 2 months.

3.2.5.2 Overall Survival (OS)

Overall survival (OS) was the key secondary endpoint of the EMERALD trial. The company submission reported results for an interim analysis (data cut 6 September 2021) and final analysis (data cut 2 September 2022) for the ESR1-mut subgroup (CS document B section 2.6.2); and results of the final analysis (data cut 2 September 2022) for post-hoc subgroups 1 and 2 (CS document B section 2.7.2.2 and 2.7.3.2 respectively). For all patients, results for an interim analysis (data cut 6 September 2021) were reported in Bidard et al., 2022 and the CSR (section 11.4.1.2) and, for the final analysis (data cut 02 September 2022), in an Overall Survival Addendum provided by the company.[11 17 20]

Interim analysis

An interim analysis of OS was performed on the same data cut (6 September 2021) as the final analysis for PFS. At this time, in the ESR1-mut subgroup, 24.3% of patients in the elacestrant arm had died and 35.4% in the SOC arm. The stratified HR was 0.59 (95% CI 0.36 to 0.96). The stratified log rank test p-value was 0.0325. At a pre-specified adjusted alpha level of 0.0001 (Table 8), the difference in OS between elacestrant and SOC was not statistically significant. Results for the interim analysis for all patients were similar (HR 0.75, 95% CI 0.54 to 1.04; p=0.0821; Bidard et al., 2022).[11]

Final Analysis

The data cut for the final OS analysis for ESR1-mut subgroup, all patients, and post-hoc subgroups 1 (ESR1 mutation) and 2 (dual mutation) was 02 September 2022.

There was no statistically significant difference in the hazard rate of death for elacestrant compared to SOC for the ESR1-mut subgroup (stratified HR 0.903, 95% CI 0.629 to 1.298; p-value =0.5823). Results were similar for all patients (stratified HR 0.912, 95% CI 0.708 to 1.175; p=0.476; Table 1 Overall Survival Addendum).[20]

Results for post-hoc analyses need to be interpreted with caution given they were not powered to detect statistical significance. There was no difference in the hazard rate of death for elacestrant compared to SOC for either post-hoc subgroup 1 (stratified HR [redacted], 95% CI [redacted] to [redacted]; p=[redacted]) or subgroup 2 (stratified HR [redacted], 95% CI [redacted] to [redacted]; p=[redacted]).

3.2.5.3 HRQoL outcomes

Data on EQ-5D-5L were reported in CS document B. section 2.6.4 (patients with ESR1-mut), CS document B section 2.7.2.3 and Appendix E .2.1.1 (post-hoc subgroup 1 (ESR1 mutation)) and CS document B section 2.7.3.3 and Appendix E.3.1.1 (post-hoc subgroup 2 (dual mutation)).

There are two main issues concerning missing data for the EQ-5D-5L index score for the ESR1-mut subgroup presented in the sections of the CS listed above (i.e. they do **not** apply to the EQ-5D analysis that was used to inform the economic model), which impact on their relevance for this appraisal. First, the company decided to obtain EQ-5D-5L index scores only for countries in which the validated tool was available (5 out of 17 countries enrolled in the trial; see company clarification response A5). For the ESR1-mut subgroup this resulted in just under half of patients in each arm having an EQ-5D-5L index score. Second, there is a difference in the total number of patients with ESR-mut 1 enrolled in four (France, Spain, UK and USA; CSR Table 14.1.1.2) of the five countries and those that had a baseline EQ-5D-5L score (CSR Table 14.2.6.4.1). These issues are described in more detail in section 3.2.2 of this report.

For completeness, the EAG report the company's findings for EQ-5D-5L index score. Namely, the CS (document B section 2.6.4) reports that EQ-5D-5L index scores for ESR-mut subgroup were similar between elacestrant and SOC at end of treatment, with no changes within groups over time. Results were similar for all patients (CS document B section 2.6.4) and for post-hoc subgroups 1 (ESR1 mutation) and 2 (dual mutation) (CS Appendix E

section 2.1.1 and section 3.1.1 respectively). However, given the issues with missing data for this outcome, the EAG considers these findings irrelevant for decision making purpose*s.* See section 4.2.5.2 below for discussion of the utility analysis of EQ-5D-5L index scores that informed the company's economic model, which used a more complete data set.

3.2.5.4 Subgroup analyses

CS Appendix E Figure 3 reports a forest plot of pre-specified subgroup analyses for the primary outcome of blinded IRC-assessed PFS for the ESR1 mut subgroup only at the 6th September 2021 data cut.

Subgroups included:

- **baseline demographic characteristics** (age (<65 years, ≥65 years, <75 years, ≥75 years), race, region),
- **measures of base disease status** (presence of visceral metastasis, baseline ECOG Performance Status, measurable disease at baseline) and
- **prior treatment** (prior treatment with fulvestrant, number of prior lines of endocrine therapy in the advanced/metastatic setting, number of lines of chemotherapy in the advanced/metastatic setting).

In CS Appendix E.1 the company state hazard ratios in patients with ESR1-mut across all pre-specified subgroups numerically favoured elacestrant and demonstrated consistency with the primary endpoint PFS (HR 0.531, 95% CI 0.378 to 0.743). The EAG agree that the point estimates for the hazard ratios were less than one, signifying a reduction in risk of disease progression or death, however, 95% confidence intervals for the following subgroups crossed 1:

Table 12 Pre-specified subgroup analyses of blinded IRC-assessed PFS in all patients with ESR1 mut where 95% CI crossed 1

Pre-specified subgroup	Hazard Ratio (95% CI)
Demographics	
Age: ≥75 years	0.514 (0.193 to 1.273)
Race: Asian	0.891 (0.122 to 4.652)
Race: other	0.289 (0.040 to 1.503)
Region: Europe	0.624 (0.386 to 1.011)
Region: Asia	0.552 (0.149 to 1.678)
Measures of base disease status	
Measurable disease at baseline: no	0.834 (0.333 to 2.178)

Pre-specified subgroup	Hazard Ratio (95% CI)
Presence of visceral metastasis: no	0.736 (0.381 to 1.443)
Prior treatment	
Prior treatment with fulvestrant: yes	0.621 (0.297 to 1.257)
Number of lines of chemotherapy in advanced or metastatic setting: 1	0.696 (0.358 to 1.308)

Source: Partly reproduced from CS Appendix E Figure 3
Abbreviations: CI, confidence interval; ESR1, oestrogen receptor 1 gene; IRC, imaging review committee; mut, mutation; PFS, progression-free survival

Caution however, is required in the interpretation of the results of these subgroup analyses given that the trial was not powered to demonstrate statistically significant treatment differences according to subgroups. Furthermore, some HRs, and their 95% confidence intervals, are calculated based on low numbers of events.

3.2.5.5 Safety outcomes

Data on adverse were reported in CS document B section 2.10 (both for all patients and for patients with ESR1-mut), CS document B section 2.7.2.3 and Appendix E .2.2 (post-hoc subgroup 1 (ESR1 mutation)) and CS document B section 2.7.3.3 and Appendix E.3.2 (post-hoc subgroup 2 (dual mutation)).

The majority of patients (>84%) in both the elacestrant and SOC arms in all patients, ESR1-mut subgroup, and post-hoc subgroups 1 and 2 experienced treatment emergent adverse events (see Table 13 and Table 14). The most common adverse event for patients receiving elacestrant was nausea, which was consistent for all patients, ESR1-mut subgroup, and post-hoc subgroups 1 and 2 (35.0%, 34.8%, 38.5% and [redacted] respectively; see Table 13 and Table 14). The most common adverse event for the SOC group differed between patient populations: for all patients nausea and fatigue (both 19.1%), for ESR1-mut subgroup fatigue (19.8%), for post-hoc subgroup 1 [redacted] and post-hoc subgroup 2 [redacted]. The proportion of patients experiencing adverse events with a severity grade ≥ 3 was similar between elacestrant and SOC for all patients, ESR1-mut subgroup, [redacted] (see Table 13 and Table 14).

The proportion of patients who experienced adverse events leading to dose interruption was greater in the elacestrant group compared to the SOC groups for all patients, ESR1-mut subgroup, [redacted] (see Table 13 and Table 14).

Treatment-related adverse events, serious adverse events, fatal events and adverse events leading to discontinuation were reported for all patients and for the ESR1-mut subgroup only (see Table 13). The findings for these adverse events were consistent between all patients and the ESR1- mut subgroup. Briefly,

- A similarly higher proportion of events were considered treatment related in the elacestrant group (63.3% and 61.7%) compared to the SOC group (43.5% and 46.2%).
- A similar proportion of patients experienced serious adverse events in the elacestrant group (12.2% and 12.2%) compared to the SOC group (10.9% and 11.3%).
- There were a small number of fatal events in the elacestrant group (1.7% and 2.6%) and SOC group (2.6% and 0.9) with none of the deaths considered treatment related.
- A similar proportion of patients experienced adverse events that led to discontinuation in the elacestrant group (6.3% and 5.2%) compared to the SOC group (4.3% and 3.8%)

Table 13 Summary of adverse events for the All patients and for ESR1-mut subgroup

Adverse event (AE)	All Patients		ESR1-mut	
	Elacestrant N=237 n (%)	SOC N=230 n (%)	Elacestrant N=115 n (%)	SOC N=106 n (%)
Any TEAE	218 (92.0)	198 (86.1)	105 (91.3)	92 (86.8)
Treatment related AE	150 (63.3)	100 (43.5)	71 (61.7)	49 (46.2)
Grade ≥3	64 (27.0)	48 (20.9)	32 (27.8)	23 (21.7)
Serious AE	29 (12.2)	25 (10.9)	14 (12.2)	12 (11.3)
Fatal events	4 (1.7)	6 (2.6)	3 (2.6)	1 (0.9)
AE leading to discontinuation	15 (6.3)	10 (4.3)	6 (5.2)	4 (3.8)
AE leading dose interruption	36 (15.2)	12 (5.2)	25 (21.7)	7 (6.6)
AE reported in ≥ 10% of patients in either trial arm				
Nausea	83 (35.0)	44 (19.1)	40 (34.8)	19 (17.9)
Arthralgia	34 (14.3)	37 (16.1)	23 (20.0)	19 (17.9)
Vomiting	45 (19.0)	20 (8.7)	21 (18.3)	10 (9.4)
Fatigue	45 (19.0)	44 (19.1)	20 (17.4)	21 (19.8)
Decreased appetite	35 (14.8)	22 (9.6)	19 (16.5)	8 (7.5)
Diarrhoea	33 (13.9)	23 (10.0)	17 (14.8)	13 (12.3)

Adverse event (AE)	All Patients		ESR1-mut	
	Elacestrant N=237 n (%)	SOC N=230 n (%)	Elacestrant N=115 n (%)	SOC N=106 n (%)
Back pain	33 (13.9)	22 (9.6)	16 (13.9)	9 (8.5)
Headache	29 (12.2)	26 (11.3)	15 (13.0)	11 (10.4)
Dyspepsia	24 (10.1)	6 (2.6)	13 (11.3)	3 (2.8)
Insomnia	18 (7.6)	11 (4.8)	13 (11.3)	7 (6.6)
Constipation	29 (12.2)	15 (6.5)	12 (10.4)	8 (7.5)
Aspartate aminotransferase increased	31 (13.1)	29 (12.6)	12 (10.4)	15 (14.2)
Anaemia	22 (9.3)	17 (7.4)	11 (9.6)	11 (10.4)
Hot flush	27 (11.4)	19 (8.3)	11 (9.6)	8 (7.5)
Alanine aminotransferase increased	22 (9.3)	24 (10.4)	6 (5.2)	13 (12.3)

Source: Partly reproduced from CS document B Table 31
Abbreviations: AE, adverse event; ESR1, oestrogen receptor 1 gene; mut, mutation; n, number of patients with the observed characteristic; N, total number in group; PFS, progression-free survival; SOC, standard of SOC, standard of care; TEAE, treatment-emergent adverse event

Table 14 Summary of adverse events for post-hoc subgroups 1 (ESR1 mutation) and 2 (dual mutation)

Adverse event (AE)	Post-hoc subgroup 1 (ESR1 mutation)		Post-hoc subgroup 2 (dual mutation)	
	Elacestrant N=78 n (%)	SOC N=75 n (%)	Elacestrant N=27 n (%)	SOC N=32 n (%)
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Grade ≥3 in ≥ 2% of patients	[redacted]	[redacted]	[redacted]	[redacted]
AE leading dose interruption	[redacted]	[redacted]	[redacted]	[redacted]
AE reported in ≥ 10% of patients in either trial arm				
Nausea	30 (38.5)	11 (14.7)	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	16 (20.5)	6 (8)	[redacted]	[redacted]
Diarrhoea	16 (20.5)	9 (12)	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]

Adverse event (AE)	Post-hoc subgroup 1 (ESR1 mutation)		Post-hoc subgroup 2 (dual mutation)	
	Elacestrant N=78 n (%)	SOC N=75 n (%)	Elacestrant N=27 n (%)	SOC N=32 n (%)
Headache	13 (16.7)	9 (12)	[redacted]	[redacted]
Decreased appetite	12 (15.4)	5 (6.7)	[redacted]	[redacted]
Dyspepsia	10 (12.8)	3 (4)	[redacted]	[redacted]
Hot flush	9 (11.5)	7 (9.3)	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Blood cholesterol increased	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Blood glucose increased	[redacted]	[redacted]	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal pain	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]

Source: Partly reproduced from CS Appendix E Table 11, Table 12, Table 15 and Table 16
Abbreviations: AE, adverse event; ESR1, oestrogen receptor 1 gene; mut, mutation; n, number of patients with the observed characteristic; N, total number in group; PFS, progression-free survival; SOC, standard of SOC, standard of care; TEAE, treatment-emergent adverse event

3.2.6 Pairwise meta-analysis of intervention studies

CS section B.2.8. states that since only one trial of elacestrant relevant to this NICE appraisal is available (i.e. the EMERALD trial) it is therefore not possible to conduct meta-analysis currently. The EAG concurs with this assertion.

3.3 Critique of studies included in the indirect treatment comparison

3.3.1 Rationale for the indirect treatment comparison

As mentioned earlier (section 3.2.1), the pivotal EMERALD trial compared elacestrant against standard of care endocrine monotherapy, comprising either fulvestrant or an aromatase inhibitor (anastrozole, letrozole, or exemestane) chosen by investigators at each study centre. None of the treatments in the comparator arm of the trial match the company's

chosen comparators in the decision problem (i.e. everolimus plus exemestane, or alpelisib plus fulvestrant). For this reason, an indirect treatment comparison was required to provide comparative efficacy estimates for elacestrant in the company's proposed subgroup patients with an ESR1-mutation who have disease progression following ≥12 months prior treatment with ET + CDK4/6i.

3.3.2 Identification, selection and feasibility assessment of studies for the indirect treatment comparison

In addition to studies of the efficacy and safety elacestrant, the company's "global clinical SLR" was designed to identify any treatments relevant to the decision problem. These included endocrine therapy, CDK4/6 inhibitors, and chemotherapy.

Neither everolimus plus exemestane, or alpelisib plus fulvestrant are indicated for patients with the ESR1 mutation and, unsurprisingly, the company's SLR didn't identify any trials of these treatments in patients relevant to the decision problem (i.e. ESR1-mutation patients treated with ≥12 months of prior ET + CDK4/6i) which could be included in an indirect treatment comparison. For this reason the company decided to use matching-adjusted indirect comparison (MAIC) methodology, informed by the individual patient data from the EMERALD trial and aggregated data from a source of real-world evidence. The CS states their approach is aligned with the core principles outlined in the NICE real-world evidence framework, though no further detail is given specifically on how the framework was applied, nor is a definition of real-world evidence given.

Few details of the search for real-world evidence are provided in the CS. The CS states that due to the absence of ESR1 mutation testing in the UK they searched for real-world evidence sources "outside the UK and Europe" (CS page 82). It is not stated whether ESR1 mutation testing is done elsewhere in Europe and whether (non-UK) European sources were searched. In response to an EAG clarification question the company stated that no European datasets were found which reported the ESR1-mutation status of patients (clarification question A11). Consequently a "targeted literature review" was performed for electronic health record real-world data sources in the United States (US). They do not state whether searches were done for real-world evidence elsewhere other than Europe and the US.

The EAG has summarised the company's criteria for selecting a real-world evidence source – specifically a registry of patient health records - in Table 15 below. As we comment, some of the criteria are not fully defined and the process by which these were assessed is not

specified. However, the EAG recognises that a pragmatic approach may be needed when there is limited choice of evidence available.

Table 15 The company's criteria for selecting real-world evidence

Criterion	EAG comment
"The primary criterion was the detailed and accurate documentation of ESR1-mutations."	This is appropriate to the elacestrant marketing authorisation, i.e. treatment of patients with the ESR1-mutation.
"A sufficiently large sample size to ensure statistical validity and robustness".	There is no indication of how many patients would be needed to fulfil this criterion.
"Accuracy of mutation documentation and treatment records"	It is not stated how accuracy was demonstrated. For example, whether based on standard database quality assurance procedures, or whether the company performed checks of their own.
"Compliance with all relevant data protection regulations and ethical standards"	The regulations and standards are not specified, but we presume the company checked these with the database owners.

Source: Partly reproduced from company's response to EAG clarification question A11.

Two US databases were considered by the company as potential evidence sources for the ITC: **Patient360 Breast** (ConcertAI) and the **Flatiron Health Clinico-Genomic Database** (FLATIRON HEALTH). The CS does not mention if any other US databases were considered. Of the two options, the company chose the Flatiron database to inform their analysis. The CS describes Flatiron as "*a real-world database which gathers clinical data from electronic health records filled by cancer care providers across the US*" (page 82). In response to clarification question A11 the company state they chose Flatiron due to its:

- Larger sample of patients meeting the inclusion criteria for this study (the EAG presumes they mean the decision problem for this NICE appraisal),
- Greater number of patients who received everolimus and exemestane as second or third-line therapy;
- Robustness and its "*regulatory-grade quality and proven acceptability"*

EAG comment

The company's justification for an indirect treatment comparison is appropriate. The EAG agrees that a matched adjusted indirect treatment comparison (MAIC) is appropriate given the specific patient population in the decision problem. The EAG recognises the necessity to use real-world evidence for the comparator treatments (due to a lack of suitable clinical trial data), however, this introduces an additional level of uncertainty to the indirect treatment comparison. Limited detail is given about the company's search for a suitable patient health record database for the comparator treatments. The database selected by the company was one of two sources identified by a targeted search in the US. It is unclear whether any other potentially relevant sources are available, hence a more systematic search on a global scale would have been preferred.

3.4 Critique of the methods and procedures for conducting the MAIC

The process followed by the company to construct and implement the MAIC involved a series of steps. We discuss and critique these in the sub-sections below.

3.4.1 Application of the inclusion criteria for the Flatiron database to the EMERALD trial

The company selected patients from Flatiron according to criteria aligned to the EMERALD trial including: confirmed diagnosis of breast cancer; evidence of ER+/HER2; tested positive for ESR1-mutation any time before or within 28 days after the start date of index line; diagnosis at stage III unresectable/stage IV (or earlier diagnosis); evidence of treatment with endocrine therapy or a CDK6/4 inhibitor in first line and/or second line.

In addition to the above, patients had to have received everolimus and exemestane or alpelisib and fulvestrant in second line and/or third line in the advanced/metastatic setting. It is not explicitly stated how patients who had disease progression following ≥12 months prior treatment with endocrine therapy and CDK6/4 inhibitor were identified in Flatiron, but the EAG notes that outcome data (OS and PFS) are stratified by CDK4/6 inhibitor exposure time. In the absence of information on how duration of previous endocrine therapy was identified the EAG assumes that exposure time for previous CDK6/4 inhibitor treatment = exposure time for previous endocrine therapy since, in practice, CDK6/4 inhibitor is usually given in combination with endocrine therapy. Importantly, disease progression on previous CDK4/6i treatment in combination with fulvestrant or an aromatase inhibitor was an inclusion criterion for the EMERALD trial. Hence, reassurance is needed that the relevant patients were accurately identified from Flatiron.

3.4.2 Identification of prognostic factors and treatment effect modifiers to be included in the MAIC

The CS presents a list of 14 prognostic factors and treatment effect modifiers (with no distinction between the two) identified by "key opinion leaders" (CS Table 5). There is no further detail given on the key opinion leaders (e.g. how many were consulted; their professional background/speciality/position; their geographical location) or the process by which they identified the prognostic factors and treatment effect modifiers (e.g. based on clinical experience and/or empirical evidence; Delphi-consensus setting exercise). It is not clear whether the key opinion leaders is the same group of UK expert clinicians who the company consulted regarding the position of elacestrant in the care pathway.

The factors identified as prognostic included patient characteristics (namely, age and menopausal status); ECOG performance status; metastases (e.g. bone, visceral); previous treatment history (e.g. number of treatment lines in the metastatic setting, prior chemotherapy); cancer diagnosis (e.g. de novo advanced/metastatic vs. recurrent disease (adjuvant)). Of the 14 prognostic factors and treatment effect modifiers identified (CS Table 5), only three had data available to enable them to be included in the MAIC for the purpose of matching patients from EMERALD to Flatiron. These were:

- **Age** (50 years and older),
- **Prior endocrine therapy** (number of lines), and
- **Prior chemotherapy** status.

Additionally, three further prognostic factors were "partially" included in the MAIC:

- **Menopausal status** –assumed based on age restriction to patients 50 years old or greater from Flatiron (proxy measure).
- **Length of time on prior CDK4/6i** –"implicitly through population restriction (prior CDK4/6i ≥12 months)".
- **Oestrogen receptor expression** – "implicitly" included through focus on the ESR1 mutation.

The CS also comments that approximately 25% of patients in the Flatiron MAIC populations were missing ECOG performance status data. To address this the company did a sensitivity analysis redistributing patients without an ECOG performance status to the known categories (i.e. ECOG performance status of 0, 1, 2 etc). It is not stated what proportions of these patients were assigned to the ECOG categories, for example, whether weighting was

proportional to the relative size of each existing category. The company state that the sensitivity analysis showed similar results observed to the base case, though no data are provided to substantiate this.

The EAG is aware of at least one published systematic review of prognostic factors in with ER+/HER2-, locally advanced/metastatic breast cancer (Cuyún Carter et al., 2021)[21]. This review (which is not cited in the CS) included 79 studies and identified a set of prognostic factors associated with worse OS and worse PFS, based on the strongest evidence from their review. Table 48 in Appendix 2 of this EAG report lists the adverse prognostic factors identified by Cuyún Carter et al (2021)[21] alongside those proposed by key opinion leaders consulted by the company, in the style of a matrix. It can be seen that there is reasonable agreement between the Cuyún Carter review and the key opinion leaders in choice of factors, but there was also a handful of prognostic factors unique to each respective source. It is noticeable that only a minority of all these prognostic factors were included in the MAIC. Amongst the factors which were not matched due to lack of data were some of notable importance such as bone metastases / bone metastases only; number of metastatic sites and de novo vs. recurrent/progressed disease. Their omission is a key limitation of the MAIC.

3.4.3 Estimation of the weights for EMERALD patients

The CS reports brief details of the weighting process. A logistic regression model was used based "*on a similar approach to propensity score weighting*" (CS page 83).

3.4.4 Comparison of weighted-elacestrant and comparator patient characteristics

CS Table 26 gives the characteristics of elacestrant-treated patients before and after weighting compared to the characteristics of patients receiving everolimus + exemestane in Flatiron (subgroup 1). The characteristics listed are the prognostic factors identified by key opinion leaders, as discussed above (e.g. age/menopausal status; number of lines of previous endocrine therapy; prior chemotherapy)(section 3.4.2). After weighting, the effective sample size for elacestrant was reduced from 78 [redacted] patients ([redacted] of the initial sample size), compared to 32 comparator patients. Importantly, however, there are some imbalances in characteristics between the elacestrant and the everolimus + exemestane arms. For example, the percentage of elacestrant patients with ECOG 0 was twice that of comparator patients, though this is explained by missing data on ECOG status for 25% of comparator patients in Flatiron. The company adjusted for the missing data in a sensitivity analysis but did not report the adjusted distribution of patients across the known ECOG categories or the results of the sensitivity analysis, other than commenting that it had *"similar*

results observed to the base case" (CS page 85). This remains as an uncertainty in the EAG's view.

CS Table 28 gives the characteristics of elacestrant-treated patients before and after weighting compared to the characteristics of patients receiving alpelisib + fulvestrant in Flatiron (subgroup 2). After weighting, the effective sample size for elacestrant reduced from 27 [redacted] patients [redacted] of the initial sample size), compared to 33 comparator patients. Again, the missing ECOG performance status score data for 25% of patients from Flatiron meant that there were imbalances between elacestrant and comparator arms. There was also disparity between the arms for the percentage of patients who had previously received chemotherapy in the advanced/metastatic setting (higher in the comparator arm).

3.4.5 Statistical methods for the MAIC

The company reported that the MAIC was constructed following methodological guidance regarding population-adjusted indirect comparisons set out in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 which deals with survival analysis and extrapolation from patient level data (company response to clarification question A12). They comment that although the guidance is applicable to data from randomised trials, they applied the same principles to the observational real-world evidence. For example, they sought real-world data for patients who most closely matched the population covered by the marketing authorisation for elacestrant.

The MAIC was built using R software, and the programming code was supplied to the EAG (company response to clarification question A13).

No further detail on the statistical methods is given, aside from that mentioned above (section 3.3 and sections 3.4.1 to 3.4.5).

EAG comment on the methods for the MAIC

The MAIC was produced according to methodological guidance from the NICE Decision Support Unit (DSU) Technical Support Document (TSD) on methods for population-adjusted indirect comparisons in submission to NICE. As far as the EAG can tell from the company's description of the MAIC, the methods were implemented appropriately. However, the MAIC suffers from some key limitations. For example, the selection of prognostic factors was poorly described and many of the factors identified could not be included in the matching of EMERALD trial patients to Flatiron database patients due to lack of available data. Furthermore, following weighting, the number of patients in the

analyses was reduced, with some imbalances in weighted prognostic factors between elacestrant and the comparator, particularly evident in post hoc subgroup 2.

3.5 Results of the MAIC

3.5.1 Progression free survival (PFS)

The CS provides Kaplan Meier PFS curves from the MAIC for elacestrant (weighted and unweighted) compared to everolimus + exemestane for subgroup 1 (patients with ESR1-mutation who have disease progression following ≥12 months prior treatment with ET + CDK4/6i) (CS Figure 17). The analyses indicate [redacted] PFS for elacestrant compared to everolimus + exemestane, with separation of the survival curves evident after the first few months and remaining so for the rest of the follow-up period (approximately 30 months). Table 16 below gives the median PFS (in months) and HR from the MAIC. The HR of 0.59 (0.36 to 0.96) indicates increased PFS associated with elacestrant, and the confidence intervals do not cross 1. However, due to the methodological limitations in the MAIC, as discussed above, inferences of statistical significance should not be made.

Table 16 MAIC PFS, elacestrant versus everolimus + exemestane (subgroup 1)

Outcome	Median (95% CI)		HR[a]
	Elacestrant weighted	Everolimus + exemestane	
PFS	[redacted]	[redacted]	0.59 (0.36, 0.96)

Source: Reproduced from CS Table 27.
[a] HR elacestrant vs everolimus + exemestane
[b] Months

CS Figure 19 provides Kaplan Meier PFS curves from the MAIC for elacestrant (weighted and unweighted) compared to alpelisib + fulvestrant for subgroup 2 (dual ESR1 and PIK3CA mutation). Initially, PFS is [redacted] for alpelisib + fulvestrant until around month 6, when the [redacted] and the [redacted]. For much of the remaining follow-up period (approximately 30 months) the curves [redacted] several times. Table 17 below gives the median PFS and HR from the MAIC. The confidence intervals are wide, notably so for the HR of 1.05 (0.50, 2.20) suggesting much uncertainty in the treatment effect. The CS describes the PFS results as [redacted] between elacestrant and alpelisib + fulvestrant. The EAG notes that they do appear [redacted], but there is insufficient evidence to conclude [redacted] between the treatments. Caution is advised in the interpretation of the results due to the methodological limitations of this analysis, as we have discussed above (section 3.3 and section 3.4).

Table 17 MAIC PFS, elacestrant versus alpelisib + fulvestrant (subgroup 2)

Outcome	Median (95% CI)		HR[a]
	Elacestrant weighted	Alpelisib + fulvestrant	
PFS	[redacted]	[redacted]	1.05 (0.50, 2.20)

Source: Reproduced from CS Table 29.
[a] HR elacestrant vs everolimus + exemestane
[b] Months

3.5.2 Overall survival (OS)

CS Figure 16 provides Kaplan Meier OS curves from the MAIC for elacestrant (weighted and unweighted) compared to everolimus + exemestane for subgroup 1 (patients with ESR1-mutation who have disease progression following ≥12 months prior treatment with ET + CDK4/6i). The curves indicate [redacted] OS for elacestrant until around month 34 when the curves cross, indicating violation of the proportional hazards assumption. Table 18 below gives median OS (in months) and HR from the MAIC, which indicate increased OS associated with elacestrant. However, due to the methodological limitations in the MAIC, as discussed above, inferences of statistical significance should not be made.

Table 18 MAIC OS, elacestrant versus everolimus + exemestane (subgroup 1)

	Median (95% CI)		HR[a]
	Elacestrant weighted	Everolimus + exemestane	
OS	[redacted]	[redacted]	0.64 (0.35, 1.16)

Source: Reproduced from CS Table 27.
[a] HR elacestrant vs everolimus + exemestane
[b] Months
[c] The CS defines NR as “not reported”, but the EAG suggests this is an error and that NR in this context should mean “not reached”

CS Figure 18 provides Kaplan Meier OS curves from the MAIC for elacestrant (weighted and unweighted) compared to alpelisib + fulvestrant for subgroup 2 (dual ESR1 and PIK3CA mutation). After around 12 months the curves separate, indicating greater OS for elacestrant, before overlapping again after month 30. Due to the overlapping curves the proportional hazards assumption cannot be supported. Table 18 below gives median OS (in months) and HR from the MAIC, which indicate a small increase in OS associated with elacestrant. However, due to the methodological limitations in the MAIC, as discussed above, inferences of statistical significance should not be made.

Table 19 MAIC OS, elacestrant versus alpelisib + fulvestrant (subgroup 2)

	Median (95% CI)		HR[a]
	Elacestrant weighted	**Alpelisib + fulvestrant**	
OS	[redacted]	[redacted]	0.80 (0.33, 1.92)

Source: Reproduced from CS Table 27.
[a] HR elacestrant vs everolimus + exemestane
[b] Months
NR, Not reached

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The company conducted a combined search for health economic literature, including cost-effectiveness studies and estimates of health-related quality of life (HRQoL), resource use and costs. We consider that the search strategy was appropriate but note that the searches are out of date as the latest update search was conducted in April 2023 (CS B.3.1 and Appendix G). One cost-effectiveness study was included in the company's review; the analysis conducted for the NICE technology appraisal of alpelisib with fulvestrant for HR+, HER2-negative, PIK3CA-mutated advanced breast cancer (TA816, 2022).[8] The company argues that TA816 is the most relevant previous NICE appraisal and outlines key features of the TA816 economic analysis in CS Table 38 and Appendix Table 26.

The EAG conducted targeted searches in PubMed and Google scholar and identified two recent economic studies that included elacestrant:

- **Vidal et al. 2023** estimated the number of clinical and resource use events associated with treating patients with elacestrant rather than standard care over a three-year time horizon.[22] We do not consider this study further as it is not an economic evaluation, and it is only reported as a conference poster with limited detail.

- **Zeng et al. 2023** reported a cost-effectiveness analysis of elacestrant versus standard endocrine therapy for second and third-line treatment of patients with advanced HR+/HER2- advanced breast cancer from a US payer perspective.[23] This used a partitioned-survival model with survival curves fitted to digitised Kaplan-Meier data from the EMERALD trial, similar to the company's approach. However, the results are not comparable due to differences in the study populations and comparators. Zeng et al. estimated cost-effectiveness for the whole EMERALD trial population and the subgroup with ESR1 mutation and used the 'investigator's choice' control arm from EMERALD and fulvestrant alone as comparators.

4.2 Summary and critique of the company's submitted economic evaluation

4.2.1 NICE reference case checklist

The company list key features of their analysis in CS B.3.2.2.3. The EAG considers that the company's analysis is consistent with the NICE reference case (see Table 20 below).[24] We note two potential areas of confusion in the company's reporting of base case cost-effectiveness results (CS Tables 81 and 82):

- The standard discount rate of 3.5% is applied to costs and QALYs, but not to life years gained (LYG), which is not stated in the tables or footnotes. We report discounted LYG for the company's base case in section 5.1 below.
- The company apply a decision modifier severity weight of 1.2 to the incremental QALYs and ICERs for Subgroup 1. We consider it more appropriate to first report results without the QALY weight, and then show how these results change with the weight, as it is a matter for the committee to consider whether the QALY weighting should be used. In the results sections 5 and 6 below, we report total and incremental QALYs without the severity weight, and we report ICERs both without and with the severity weight applied. We critique the company's absolute and proportional QALY shortfall calculations in section 7.

Table 20 NICE reference case checklist

Element of HTA	Reference case	Is the company analysis consistent with reference case criteria?
Perspective on outcomes	All health effects, whether for patients or, when relevant, carers	Yes (no direct health effects assumed for carers)
Perspective on costs	NHS and personal social services (PSS)	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes (lifetime horizon)
Synthesis of evidence on health effects	Based on systematic review	Yes

Element of HTA	Reference case	Is the company analysis consistent with reference case criteria?
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients or carers, or both	Yes (EQ-5D-5L data from EMERALD trial). See section 4.2.5.2 below.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes (UK tariff, Hernández-Alava formula)[25]
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit, except in specific circumstances	Yes (QALY weight of 1.2 applied for Subgroup 1. No QALY weight applied to the dual mutated subgroup) See Section 7 below.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes, for costs and QALYs (no discounting applied to LYs reported in the CS)

Source: Produced by the EAG based on information in CS section B.3 and Table 38

4.2.2 Model decision problem

4.2.2.1 Population

The company reports cost-effectiveness results for two subgroups:

- Subgroup 1 (target population): *ESR1-mut* + ≥12 months prior ET with CDK4/6i
- Subgroup 2 (dual mutated): *ESR1-mut+PIK3CA-mut* + ≥12 months ET with CDK4/6i

The company's target population for elacestrant is restricted to the subgroup of the licensed population with disease progression after at least 12 months of endocrine therapy with CDK4/6 inhibitors. They state that this will provide best value in UK clinical practice (CS B.3.2.1), based on clinical feedback informed by the post hoc subgroup analyses of EMERALD trial data by duration of prior treatment (Bardia 2023, Menarini 2024).[9] [14] See section 3.2.5.4 above for the EAG description and critique of this subgroup analysis.

Baseline characteristics for these subgroups in the EMERALD trial and Flatiron cohorts are reported in CS Tables 20 and 26, respectively. For the base case economic analysis, the company used patient characteristics from EMERALD for both subgroups: [redacted] with mean ages [redacted] years for subgroup 1 and [redacted] years for subgroup 2 (CS Table 39). In response to clarification question B2, the company added a scenario with baseline patient characteristics from the Flatiron cohorts: [redacted] years for subgroup 1 and [redacted] for subgroup 2 (CQ response Table 5). This gave a small increase in the ICER for subgroup 1 and had a negligible impact on cost-effectiveness for subgroup 2.

4.2.2.2 Intervention and comparators

The modelled intervention is elacestrant at 345 mg orally, once daily (CS B.3.2.3.1). To account for dose interruptions and modifications in the economic model, elacestrant costs are adjusted with a relative dose intensity (RDI) estimated from the EMERALD trial (see CS B.3.5.1.1 and section 4.2.6.1 below).

The company include one comparator for each subgroup in their economic model, based on clinical advice (CS section B.3.2.3.2) that these are the most relevant current treatments in the subgroups of interest: everolimus + exemestane for the target population (subgroup 1); and alpelisib + fulvestrant for the dual mutated subgroup (subgroup 2). Other comparators specified in the NICE scope (endocrine therapy with or without chemotherapy, and chemotherapy alone) are excluded on the basis that these are rarely used in practice for the target population. Data from the control arm of the EMERALD trial (investigator's choice of fulvestrant, anastrozole, letrozole, or exemestane monotherapy) is therefore not used in the economic model. As there is no direct evidence for the effectiveness of elacestrant versus everolimus + exemestane or alpelisib + fulvestrant, and the pivotal trials for these treatments did not include the subgroups of interest (so a network meta-analysis is not feasible), the company rely on data from the Flatiron cohorts and the unanchored MAIC (CS B.2.9) to estimate survival outcomes for the economic model.

EAG conclusions on the modelled decision problem

The economic model reflects the company's target population for elacestrant, and the subgroup with dual mutations as requested in the NICE scope. As the model relies on MAIC-adjusted survival outcomes, with trial data weighted to reflect baseline prognostic factors in the Flatiron cohorts, the EAG prefers the analysis with mean ages at baseline from the Flatiron cohorts (CS Tables 20 and 26).

The EAG agrees that the focus on the comparators everolimus + exemestane for subgroup 1 and alpelisib + fulvestrant for subgroup 2 is reasonable, although endocrine therapy with or without chemotherapy, or chemotherapy alone may be used for some patients (see discussion in sections 2.2.3.2 and 2.3 above).

4.2.2.3 Perspective, time horizon and discounting

The analysis is in line with the NICE Reference Case with respect to the perspective (NHS and PSS); time horizon (lifetime); and discounting (3.5% applied to costs and QALYs).

4.2.3 Model structure and assumptions

4.2.3.1 Overview of the model structure

The company describe the structure of their economic model in CS section B.3.2.2. They use a cohort-level partitioned survival analysis (PartSA), implemented in Microsoft Excel (see CS Figures 20 and 21). The model has a one week cycle length and a lifetime horizon. A summary of model assumptions is provided in CS Table 80, and a list of the base case model parameters and probabilistic distributions in CS Table 79.

The distribution of the modelled cohort between health states is determined by survival curves fitted to time to treatment discontinuation (TTD), progression-free survival (PFS) and overall survival (OS) data from the EMERALD trial for elacestrant, and to KM curves from the Flatiron dataset for the comparators. The MAIC approach described in section 3.4 above is used to weight the data for the elacestrant arm of the EMERALD trial to improve alignment with baseline prognostic characteristics in the Flatiron cohorts (see CS Tables 26 and 28 for subgroup 1 and 2, respectively).

The model includes constraints to ensure that:

- The proportion of patients on treatment cannot exceed progression-free survival;
- The proportion who are progression-free cannot exceed overall survival; and
- The risk of death is no lower than for people of the same age and sex in the general population.

We critique the model structure and key assumptions in the following section. See section 4.2.4 below for EAG critique of the fitted TTD, PFS and OS extrapolations. Other model parameters include health-related quality of life for the progression-free and progressed disease states (section 4.2.5), and resource use and costs (section 4.2.6).

4.2.3.2 EAG critique of model structure and assumptions

The partitioned survival analysis (PartSA) modelling approach is common in cancer appraisals and provides a practical alternative to a health-state transition model when data to estimate transition probabilities is sparse. However, as described in NICE Decision Support Unit Technical Support document 19, PartSA requires two key assumptions: that the survival endpoints (TTD, PFS and OS) can be modelled and extrapolated independently; and that trends in the hazards of these endpoints from the study period persist over the time horizon.[26] The risk of bias due to these assumptions is mitigated to some extent in the company's model by the constraints applied to ensure that TTD ≤ PFS, PFS ≤ OS and the risk of mortality is no less than for people of the same age in the general population. However, careful consideration of the clinical plausibility of the survival curve extrapolations is still essential. See section 4.2.4 below for discussion on the methods used to fit TTD, PFS and OS curves for elacestrant and comparators, and the plausibility of the extrapolations.

As there is no direct evidence to compare elacestrant with everolimus + exemestane or alpelisib + fulvestrant in the company's target population and the dual-mutated subgroup, the model relies on an unanchored MAIC for estimation of survival outcomes. The economic model results are therefore vulnerable to bias from the MAIC due to the lack of data on identified prognostic factors and effect modifiers (CS Table 25 and EAG discussion in 3.4). There is also considerable uncertainty around the survival curves due to the small sample sizes for both subgroups of interest in the Flatiron datasets, and also from the elacestrant arm of the EMERALD trial (particularly for the dual mutated subgroup).

The lack of data on treatment duration in the Flatiron datasets for the comparator arms is also problematic. The company use observed data from the EMERALD trial for elacestrant but assume that TTD is equal to PFS for the comparators. It is quite common in cancer appraisals to assume that treatment continues until disease progression, and this is often reasonable. However, the use of different assumptions for the intervention and comparator is a potential source of bias, that would have a direct impact on costs and hence on the ICER. The elacestrant trial data used in the model also shows a difference between TTD and PFS, with a proportion of patients in the subgroups of interest stopping treatment before

progression. Consideration of alternative sources of data or assumptions regarding the duration of treatment for the comparators is therefore important.

Other model assumptions that are potentially important are the cost and practical impact of introducing ESR1 testing the NHS to assess suitability for elacestrant, and the mix of subsequent treatments that are used in NHS practice after disease progression.

EAG conclusions on the model structure and assumptions

- We consider that the use of a partitioned survival model is appropriate, and that the implemented model is of a high standard.
- However, we do have concerns about the robustness and plausibility of the PFS and OS extrapolations due to the reliance on an unanchored MAIC and the sparsity of data for the company's target population and the dual mutated subgroup from the EMERALD trial and the Flatiron cohorts.
- We are also concerned over the lack of data on treatment duration for the comparators, and the potential for bias from the company's assumption that treatment will always continue until disease progression in the comparator arms, whereas treatment with elacestrant can stop prior to progression (as observed in the EMERALD trial).
- We conduct additional scenario analyses to explore alternative assumptions regarding these concerns, as well as other uncertainties, including the cost of introducing ESR1 testing and NHS practice regarding subsequent treatment.

4.2.4 Clinical effectiveness and extrapolation

4.2.4.1 Overview of methods for extrapolation of survival outcomes

The economic model uses parametric survival curves for PFS, OS and TTD in the two subgroups, which are fitted to patient-level data from the EMERALD trial for elacestrant and to pseudo patient-level data derived from KM curves for the Flatiron comparator cohorts (CS B.3.3.4).[27] MAIC weights are applied to the elacestrant patient-level data to better align prognostic characteristics with those in the Flatiron cohorts (CS B.2.9.1).

The company report results for six standard parametric survival distributions (exponential, generalised gamma, Gompertz, log-logistic, log-normal and Weibull and gamma). Alternative flexible survival models are not explored. The base case distribution in each case was chosen on the basis of fit to the KM estimates, using visual inspection and Akaike and Bayesian information criteria (AIC, BIC) statistics, and consideration of the clinical plausibility

of the long-term extrapolations. The company do not report formal elicitation of survival expectations from clinical experts.

In the base case, OS and PFS curves are fitted to each dataset independently, on the grounds that the proportional hazards assumption 'may not hold' due to crossover of the elacestrant and comparator KM curves: see CS Figures 16 and 17 for subgroup 1, and Figures 18 and 19 for subgroup 2. Formal tests of proportional hazards are not reported. The company report scenario analysis with parametric OS and PFS curves fitted to the MAIC-weighted trial data for elacestrant, which are then adjusted for the comparator arms using MAIC hazard ratios (CS Tables 27 and 29).

TTD data from the EMERALD trial is mature (CS Figure 26). So for elacestrant, the company use the KM curves directly in the base case, and parametric curves fitted to the MAIC-weighted EMERALD data in scenario analysis. However, data was not available to estimate TTD for the comparator arms, as the Flatiron datasets do not include treatment duration. The company considered estimating comparator TTD from median treatment duration but could not find this reported in the literature for the particular subgroups of interest. The company therefore made an assumption, setting TTD equal to PFS for the comparator arms. The model includes an option to estimate comparator TTD by applying an assumed hazard ratio to the PFS but did not report scenario analysis using this option.

We discuss the company's assumptions and selection of survival extrapolations for their base case and scenarios below.

4.2.4.2 Survival curves for subgroup 1

CS Figures 16 and 17 show the unweighted and MAIC-weighted OS and PFS KM plots for elacestrant and everolimus + exemestane in subgroup 1. The sample size for this subgroup is moderate for elacestrant (n=78; effective sample size after MAIC adjustment n=[redacted]) and very low for everolimus + exemestane (n=32) (CS Table 26). There is therefore high uncertainty over the KM estimates, particularly for the comparator and in the later sections of follow up, as the numbers of patients at risk and the number of events are low.

The company discuss their choice of OS, PFS and TTD distributions for subgroup 1 in CS section B.3.3.4.1. We show survival extrapolation graphs for this subgroup in Appendix 3: see Figure 17 and Figure 16 for the company's base case extrapolations for elacestrant and everolimus + exemestane respectively.

4.2.4.2.1 Overall survival

Overall survival estimates and model fit statistics for the six parametric distributions in subgroup 1 are summarised in Table 21 below.

Table 21 OS extrapolations: subgroup 1

Distribution	Model fit			Survival estimates (year)				
	AIC	BIC	Rank	1	2	3	5	10
Everolimus + exemestane								
Kaplan-Meier	-	-	-	62.3%	37.5%	28.1%	14.1%	-
Exponential	173.17	174.63	1	63.7%	40.3%	25.7%	10.4%	1.1%
Gen. gamma	176.57	180.97	7	63.4%	40.3%	27.0%	13.3%	3.1%
Gompertz	175.10	178.03	5	62.7%	40.2%	26.7%	12.7%	2.9%
Log-logistic	174.32	177.25	2	62.3%	38.6%	26.6%	15.3%	6.5%
Log-normal	175.23	178.16	6	61.2%	40.2%	29.0%	17.4%	7.1%
Weibull	175.10	178.03	4	64.6%	40.1%	24.7%	9.2%	0.7%
Gamma	175.01	177.94	3	64.8%	39.8%	24.4%	9.0%	0.7%
Elacestrant (weighted to everolimus + exemestane)								
Kaplan-Meier	-	-	-	86.6%	51.6%	14.7%	-	-
Exponential	342.10	344.45	7	74.3%	54.8%	40.7%	22.5%	5.0%
Gen. gamma	334.16	341.23	5	83.8%	55.3%	26.8%	1.3%	0.0%
Gompertz	332.93	337.64	2	83.9%	56.6%	24.3%	0.1%	0.0%
Log-logistic	334.04	338.75	4	83.5%	54.6%	34.5%	15.7%	4.3%
Log-normal	337.04	341.75	6	80.5%	54.3%	37.4%	19.3%	5.4%
Weibull	332.50	337.21	1	83.8%	54.7%	29.6%	5.2%	0.0%
Gamma	333.35	338.06	3	82.8%	54.4%	32.4%	9.8%	0.3%

Source: Table collated by the EAG from CS Tables 40, 41, 46 and 47 and the company's model
Company base case distributions in bold

For everolimus + exemestane, the parametric distributions have a similar visual and statistical fit to the Flatiron KM data. Survival estimates are similar over the first 2 years, but there is then some divergence (see Figure 11 below). The distribution with the best statistical fit is the exponential (constant hazard), but the company select the gamma for their base case (the third best statistical fit), on the basis that this has the lowest 5-year survival (9%), which is closest to clinical expectations. This assessment is based on a clinical estimate of 5% five-year survival for patients with HR+, HER2- PIK3CA-mutated advanced breast cancer treated with everolimus + exemestane, as reported in the alpelisib company submission for NICE appraisal TA816.[8] We note that the alpelisib company also reported

clinical estimates of 50% and 33.3% survival 1 and 2 years, respectively (TA816 EAG report). Survival estimates from the Flatiron KM and parametric distributions in Table 21 all exceed these expectations. It is not clear if this relates to differences in the populations under consideration, and/or to other differences between the data sources.

For elacestrant, with the exception of the exponential, the visual and statistical fits and survival estimates at 1 and 2 years are similar for the different parametric distributions. However, there is a wide range of survival projections at 3 and 5 years. The Weibull gives the best statistical fit, but the company conclude that the log-normal and log-logistic curves have a good visual fit to the KM data (see Figure 12). They also argue that they expect the superiority of elacestrant over everolimus + exemestane over the first 2.5 years of follow-up to persist at 5 years. On this basis, they select the log-logistic distribution for their base case.

Figure 2below shows the OS KM estimates and fitted distributions used in the company's base case: log-logistic for elacestrant and gamma for the comparator arm. The company also report results for scenario analyses with Weibull and exponential OS extrapolations for everolimus + exemestane and gamma and log-normal extrapolations for elacestrant in subgroup 1.

EAG conclusions on OS extrapolations for subgroup 1:

- There is high uncertainty over the OS extrapolations due to the limited sample sizes (particularly for the comparator arm) and the use of an unanchored MAIC.
- We agree with the use of the gamma distribution for the comparator arm based on clinical advice on current survival expectations in this subgroup.
- Expert advice to the EAG is that 5-year survival with current treatment in this population is likely to be around 5%, and that although there may well be a small proportion of patients who gain a long-term benefit with elacestrant, this is as yet untested. We therefore conclude that the company's base case log-logistic OS extrapolation for elacestrant is overly optimistic given the current evidence base.
- For EAG analysis, we prefer to use an independent gamma OS extrapolation for elacestrant as well as for the comparator arm (Figure 3, below). The gamma has a good statistical and visual fit in both arms and similar survival projections after year 5.
- To test the impact of a wider range of OS extrapolations, we also report additional EAG scenarios using the MAIC HR option in the company's model (see 6.1.1).

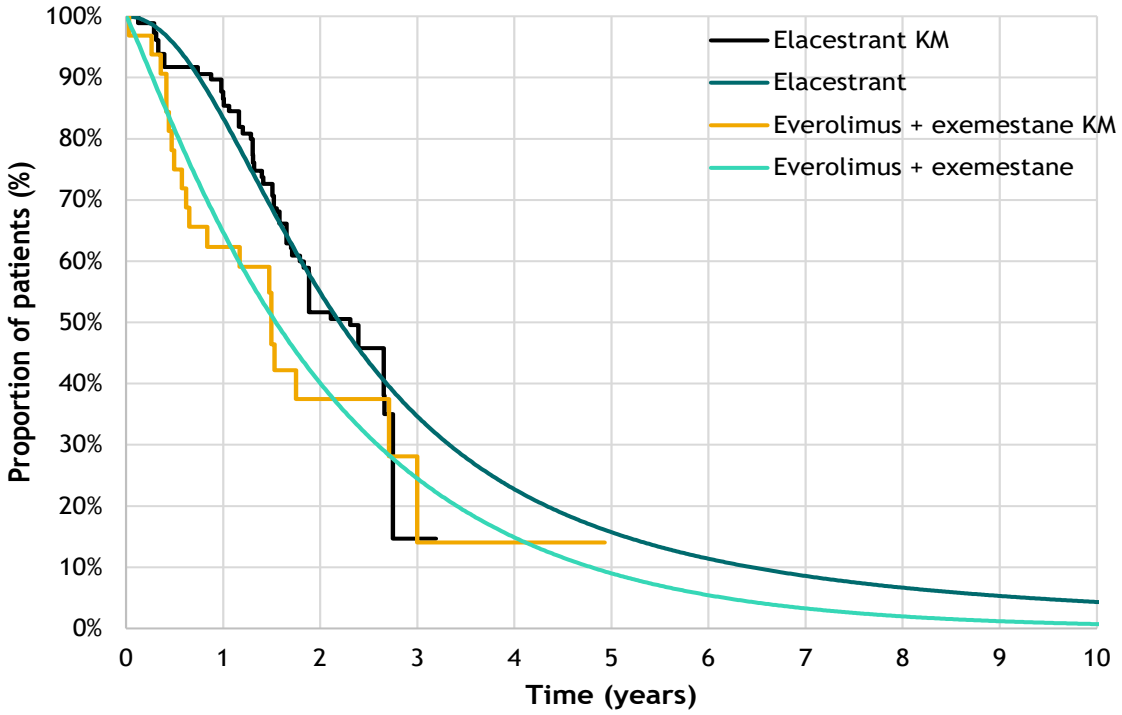

Figure 2 OS extrapolations for the company's base case: subgroup 1

Source: produced by the EAG from the company's model

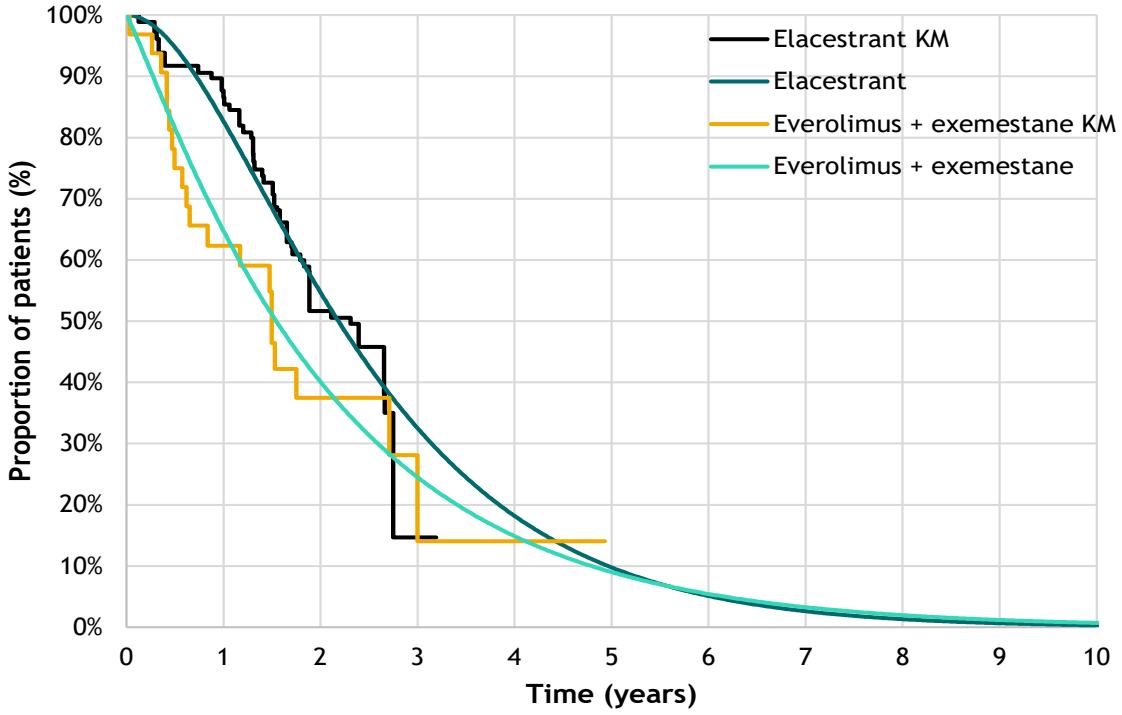

Figure 3 OS extrapolations, independent gamma for both arms: subgroup 1

Source: produced by the EAG from the company's model
Gamma extrapolation for elacestrant and everolimus + exemestane

4.2.4.2.2 Progression free survival

Statistical measures of fit and survival estimates for PFS extrapolations for subgroup 1 are summarised in Table 22.

Table 22 PFS extrapolations: subgroup 1

Distribution	Model fit			Survival estimates (year)				
	AIC	BIC	Rank	1	2	3	5	10
Everolimus + exemestane								
Kaplan-Meier	-	-	-	14.6%	-	-	-	-
Exponential	150.53	151.99	7	12.5%	1.5%	0.2%	0.0%	0.0%
Gen. gamma	146.20	150.60	5	7.2%	0.4%	0.0%	0.0%	0.0%
Gompertz	148.74	151.67	6	5.9%	0.0%	0.0%	0.0%	0.0%
Log-logistic	144.20	147.14	1	8.4%	1.8%	0.7%	0.2%	0.0%
Log-normal	144.84	147.77	3	9.0%	1.2%	0.3%	0.0%	0.0%
Weibull	145.69	148.62	4	5.5%	0.0%	0.0%	0.0%	0.0%
Gamma	144.62	147.55	2	5.9%	0.1%	0.0%	0.0%	0.0%
Elacestrant (weighted to everolimus + exemestane)								
Kaplan-Meier	-	-	-	34.3%	29.3%	-	-	-
Exponential	250.31	252.67	4	37.0%	13.4%	5.0%	0.7%	0.0%
Gen. gamma	212.37	219.44	1	31.1%	20.7%	16.5%	12.3%	8.3%
Gompertz	250.63	255.34	5	36.2%	18.4%	11.9%	7.4%	5.4%
Log-logistic	245.92	250.64	3	30.8%	14.2%	8.6%	4.4%	1.7%
Log-normal	242.02	246.73	2	32.2%	14.2%	7.8%	3.1%	0.7%
Weibull	252.31	257.02	7	37.1%	13.6%	5.1%	0.7%	0.0%
Gamma	252.13	256.84	6	36.4%	12.3%	4.2%	0.5%	0.0%

Source: Table collated by the EAG from CS Tables 42, 43, 48 and 49 and the company's model
Company base case distributions in bold

For everolimus + exemestane, all distributions give a similar fit to the KM, with the exception of exponential and Gompertz. Projected progression free survival is similar for the remaining distributions, with some patients remaining progression free at 3 years with the log-logistic and log-normal. The company select the log-normal distribution for their base case, and use log-logistic and gamma for scenario analysis.

For elacestrant, the best statistical fit is the generalised gamma, although this has a poor visual fit after the first few months and a very optimistic long-term projection (over 12% still progression free at 5 years). The log-normal and log-logistic have similar statistical and

visual fit and give similar long-term projections. The company use the log-normal for their base case, and log-logistic in a scenario.

Figure 4 PFS extrapolations for the company's base case: subgroup 1

Source: produced by the EAG from the company's model
Log-logistic extrapolation for elacestrant and log-normal for everolimus + exemestane

EAG conclusions on PFS extrapolations for subgroup 1:

- The company's base case PFS extrapolations for subgroup 1 are reasonable. We also test scenarios with Weibull for everolimus + exemestane, and exponential for elacestrant (see 6.1.1).

4.2.4.2.3 Time to treatment discontinuation

As data on time to discontinuation of elacestrant in the EMERALD trial is mature, the company used the KM curve directly in the economic model. Fitted parametric curves were included in the economic model for use in scenario analysis. See Table 23 for a summary of fit statistics and treatment continuation rates for subgroup 1. The company report results for scenarios using log-normal and log-logistic distributions for elacestrant TTD. We note that, compared with the KM estimates, all of the parametric extrapolations underestimate the proportion of patients still on elacestrant at 2 years.

Table 23 Elacestrant TTD: subgroup 1

Distribution	Model fit			Survival estimates (year)				
	AIC	BIC	Rank	1	2	3	5	10
Kaplan-Meier	-	-	-	[redacted]	[redacted]	-	-	-
Exponential	455.13	457.48	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gen. gamma	431.34	438.41	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	453.91	458.62	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	442.37	447.08	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	438.63	443.34	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	456.89	461.61	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	457.03	461.74	7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table collated by the EAG from CS Tables 44, 45 and the company's model
Company base case distributions in bold

Treatment discontinuation data is not available for the comparator everolimus + exemestane arm. The company make an assumption that for everolimus + exemestane TTD is equal to PFS. This results in broadly similar TTD curves for the two arms in the company's base case in this subgroup (see Figure 5).

EAG conclusion for TTD extrapolations in subgroup 1

We agree with the use of KM data from the EMERALD trial rather than a fitted extrapolation to estimate time to treatment duration for elacestrant. As the data is mature, this will provide the best available estimate. To further explore sensitivity to treatment duration for elacestrant, we report an additional scenario using the best-fit extrapolation (generalised gamma) for elacestrant TTD (see section 6.1.1).

We are concerned about the potential for bias due to the use of different modelling assumptions for TTD in the elacestrant and comparator arms. In practice, it is likely that some patients in the comparator arm may discontinue treatment prior to progression, as was observed for elacestrant. If so, this will result in over-estimation of treatment costs for the comparator relative to elacestrant. We explore the impact of such an effect using the option provided in the company's model to apply a hazard ratio to reduce TTD relative to PFS in the comparator arm.

Figure 5 TTD extrapolations for the company's base case: subgroup 1

Source: produced by the EAG from the company's model
KM and fitted generalised gamma distribution for elacestrant; and base case fitted distribution for PFS (log-normal) assumed for everolimus + exemestane

4.2.4.3 Survival curves for subgroup 2

CS Figures 18 and 19 show the unweighted and MAIC-weighted OS and PFS KM plots for elacestrant and alpelisib + fulvestrant in subgroup 2. The sample size for this subgroup is very low for both elacestrant (n=27; effective sample size n=[redacted]) and alpelisib + fulvestrant (n=33) (CS Table 26), so there is very high uncertainty over the KM estimates.

The company discuss their choice of OS, PFS and TTD distributions for subgroup 2 in CS section B.3.3.4.2. We show survival extrapolation graphs for this subgroup in Appendix 4. Figure 24 and Figure 23 show the company's base case extrapolations for alpelisib + fulvestrant and elacestrant respectively.

4.2.4.3.1 Overall survival

Table 24 summarises statistical measures of fit and survival estimates for OS in subgroup 2. The company report that the generalised gamma distribution did not converge. The exponential distribution has the worst statistical fit and poor visual fit to the KM in both arms (Figure 18 and Figure 19).

For alpelisib + fulvestrant, the Gompertz also has a relatively poor statistical and visual fit. The gamma distribution has the best statistical fit and a good visual fit to the KM. The other distributions all have a similar statistical and visual fit. The company chose the gamma distribution for their base case, and the Weibull and log-normal for scenario analysis.

For elacestrant, the best statistical fit is the Gompertz, but the company conclude that this is unrealistic, as it predicts [redacted]. The other distributions have a similar statistical fit, and the company chose the Weibull for their base case, and the gamma and log-normal for scenario analysis.

Table 24 OS extrapolations: subgroup 2

Distribution	Model fit			Survival estimates (year)				
	AIC	BIC	Rank	1	2	3	5	10
Alpelisib + fulvestrant								
Kaplan-Meier	-	-	-	84.7%	55.1%	34.4%	-	-
Exponential	126.69	128.18	6	76.4%	58.1%	44.4%	26.0%	6.7%
Gen. gamma	-	-	-	-	-	-	-	-
Gompertz	123.71	126.71	5	85.3%	61.4%	31.8%	0.6%	0.0%
Log-logistic	122.44	125.43	4	86.1%	56.0%	34.0%	14.1%	3.3%
Log-normal	122.33	125.32	2	84.8%	55.3%	35.3%	15.4%	2.9%
Weibull	122.33	125.32	3	86.5%	58.3%	31.8%	5.2%	0.0%
Gamma	122.14	125.13	1	86.1%	56.8%	32.7%	8.6%	0.2%
Elacestrant (weighted to everolimus + exemestane)								
Kaplan-Meier	-	-	-	88.8%	73.6%		-	-
Exponential	90.62	91.92	7	83.2%	68.9%	57.3%	39.7%	15.7%
Gen. gamma	-	-	-	-	-	-	-	-
Gompertz	88.00	90.59	1	92.5%	73.4%	37.7%	0.0%	0.0%
Log-logistic	89.17	91.76	4	91.9%	70.9%	50.3%	24.9%	6.8%
Log-normal	89.65	92.24	5	90.4%	69.7%	52.5%	30.6%	9.9%
Weibull	88.61	91.20	2	92.1%	71.0%	46.1%	11.4%	0.0%
Gamma	88.96	91.56	3	91.4%	70.4%	49.1%	20.0%	1.3%

Source: Table collated by the EAG from CS Tables 50, 51, 56 and 57 and the company's model
Company base case distributions in bold

Figure 6 OS extrapolations for the company's base case: subgroup 2

Source: Source: produced by the EAG from the company's model
Weibull extrapolation for elacestrant and Gamma for everolimus + exemestane

EAG conclusions on OS extrapolations for subgroup 2:

- We agree with the company's base case OS extrapolations of gamma for alpelisib + fulvestrant and Weibull for elacestrant in subgroup 2 (Figure 6).
- We report additional EAG scenario analyses with Gompertz, Weibull and Gamma distributions and the MAIC HR option (see 6.1.1).

4.2.4.3.2 Progression free survival

See Table 25 for a summary of model fit statistics and survival estimates for PFS in subgroup 2. The best fit for the alpelisib + fulvestrant is log-normal, followed by generalised gamma, gamma and log-logistic distributions. These distiributions provide a reasonable visual fit to the KM, and similar PFS projections. The company choose the log-normal for their base case and report scenarios with generalised gamma and gamma distributions.

The KM estimates for elacestrant are more uncertain, due to the small sample and number of observed progression events in this subgroup. The best statistical fit is the generalised gamma, but this has a poor visual fit. The company select the log-normal for their base case,

which has a good statistical and visual fit, and report scenarios with log-logistic and exponential extrapolations.

Table 25 PFS extrapolations: subgroup 2

Distribution	Model fit			Survival estimates (year)				
	AIC	BIC	Rank	1	2	3	5	10
Alpelisib + fulvestrant								
Kaplan-Meier	-	-	-	30.2%	5.0%			-
Exponential	163.80	165.29	7	27.8%	7.6%	2.1%	0.2%	0.0%
Gen. gamma	156.23	160.72	2	21.2%	5.0%	1.9%	0.5%	0.1%
Gompertz	161.48	164.47	6	28.5%	1.4%	0.0%	0.0%	0.0%
Log-logistic	156.73	159.72	4	20.3%	4.6%	1.8%	0.5%	0.1%
Log-normal	154.52	157.51	1	21.0%	3.5%	0.8%	0.1%	0.0%
Weibull	157.98	160.97	5	24.9%	1.5%	0.0%	0.0%	0.0%
Gamma	156.42	159.41	3	22.7%	1.8%	0.1%	0.0%	0.0%
Elacestrant (weighted to everolimus + exemestane)								
Kaplan-Meier	-	-	-	21.1%	-	-	-	-
Exponential	84.72	86.01	4	30.7%	9.2%	2.8%	0.3%	0.0%
Gen. gamma	73.32	77.20	1	21.5%	12.4%	9.0%	6.1%	3.5%
Gompertz	86.66	89.25	7	30.6%	10.5%	4.2%	0.9%	0.1%
Log-logistic	84.16	86.75	3	23.0%	8.5%	4.6%	2.0%	0.7%
Log-normal	82.84	85.43	2	24.3%	8.0%	3.5%	1.0%	0.1%
Weibull	86.46	89.05	6	29.8%	7.2%	1.6%	0.1%	0.0%
Gamma	86.06	88.65	5	28.4%	6.2%	1.3%	0.1%	0.0%

Source: Table collated by the EAG from CS Tables 52, 53, 58 and 59 and the company's model
Company base case distributions in bold

EAG conclusions on PFS extrapolations for subgroup 2

- We consider the company's choice of log normal PFS extrapolations for both arms in subgroup 2 (Figure 7) to be reasonable.

Figure 7 PFS extrapolations for the company's base case: subgroup 2

Source: Produced by the EAG from the company's model
Log-normal extrapolations for elacestrant and alpelisib + fulvestrant

4.2.4.3.3 Time to treatment discontinuation

Table 26 summarises fit statistics and survival estimates for elacestrant TTD for subgroup 2.

As the data are mature, the company use the KM curve directly in the base case analysis.

They also report scenarios with log-normal and log-logistic extrapolations.

Table 26 Elacestrant TTD: subgroup 2

Distribution	Model fit			Survival estimates (year)				
	AIC	BIC	Rank	1	2	3	5	10
Kaplan-Meier	-	-	-	[redacted]	[redacted]	-	-	-
Exponential	121.56	122.78	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gen. gamma	108.23	111.89	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	120.73	123.17	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	111.60	114.04	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	113.09	115.53	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	123.32	125.76	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	123.48	125.91	7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table collated by the EAG from CS Tables 54 and 55 and the company's model
Company base case distributions in bold

Due to the lack of data on treatment duration for alpelisib + fulvestrant in this subgroup, the company assume that TTD is equal to PFS (Figure 8).

Figure 8 TTD extrapolations for the company's base case: subgroup 2

Source: Produced by the EAG from the company model
KM and fitted generalised gamma distribution for elacestrant; and base case fitted distribution for PFS (log-normal) assumed for alpelisib + fulvestrant

EAG conclusion for TTD extrapolations in subgroup 2

As in subgroup 1, we agree with the direct use of the mature KM data from EMERALD to model treatment duration for elacestrant. However, the assumption that TTD is equal to PFS for the comparator arm in subgroup 2 results in a longer treatment duration for alpelisib + fulvestrant than for elacestrant, despite elacestrant having a longer projected time to progression. This is counterintuitive and we explore the use of a hazard ratio to reduce TTD relative to PFS in the comparator arm (see section 6.1.1).

4.2.5 Health related quality of life

4.2.5.1 Systematic literature review for utilities

The company conducted a systematic review to identify HRQoL utility data for patients with breast cancer (CS Appendix H). The searches were performed between January 2010 and April 2023, and the inclusion criteria are shown in CS Appendix H Table 27 and CS Appendix H Figure 9 (PRISMA diagram).

Eight studies were identified and summarised in CS Appendix H Table 28. These studies provided the health state utilities and AE disutilities used in the company's scenario analysis. Three studies referred to metastatic breast cancer: Hagiwara et al. 2018[28] conducted in Japan; Mistry et al. 2018[29] conducted in the USA; and Lloyd et al. 2006[30] conducted in the UK. The economic evaluation presented by Zeng et al. 2023 [23] (see section 4.1) used the progression-free state utility from Mistry et al. 2018 (0.837, range 0.753-0.921) and progressed disease state utility from Lloyd et al. 2006 (0.443, range 0.399-0.487), although EMERALD trial results were used to develop their model.

4.2.5.2 Study-based health related quality of life

Patients in the EMERALD trial were asked to complete the EQ-5D-5L questionnaire at study baseline, during treatment cycles, and at post-treatment, end of trial and safety follow-up assessments. EQ-5D-5L data for EMERALD patients with an ESR1 mutation were used to estimate health state utilities in the company's base case analysis (see CS B.3.4.1 and B.3.4.2, and company response to clarification question B4). We note that the utility analysis was not restricted to the company's specific target population for elacestrant (subgroup 1, ESR1-mut with at least 12 months of prior ET + CDK4/6i) and did not differentiate between subgroup 1 and the dual mutation subgroup 2.

In response to clarification question B4, the company provided further information about the data, methods and results of the utility analysis. Data for 187/228 (82%) of patients from the EMERALD trial with an ESR1 mutation were included: 222 were considered in the data preparation stage, 35 of whom were excluded due to missing data (company clarification response Table 6). The company used the NICE recommended Hernández-Alava et al. algorithm to map from EQ-5D-5L data to EQ-5D-3L UK utility values.[25]

The data were analysed using a linear mixed-effects regression to account for repeated observations (the dataset included 886 EQ-5D-5L observations from 187 patients). The utility regression model estimated the relationship between the EQ-5D utility score, progression status, concurrent adverse events, three baseline co-variates (age, utility and

number of prior lines of therapy), and patient ID as the random effect term (company clarication response Table 7). The company note that they also considered including treatment arm, but that this was likely to be correlated with adverse events.

Simple descriptive statistics for utility by health state are reported in CS Table 61. The regression coefficient estimates are reported in Table 8 of the company's clarification response, and residual plots in Figure 1. Predicted health state utilities from the regression model are reported in CS Table 62: progression-free [redacted] (95% CI: [redacted]) and progressed disease [redacted] (95% CI: [redacted]. These values are used in the company's model for the base case analysis.

4.2.5.3 Adverse event disutilities

The company considered adverse events grade 3+ with an incidence of at least 2% for elacestrant or the comparators (CS B.3.4.4). As the utility regression equation included an AE term, the company did not include AE disutilities in their base case, but they did include them in scenario analyses, applied as a one-off QALY decrement by treatment arm. CS Table 63 shows the AE frequencies and Table 64 the disutility values, durations and sources. In response to clarification questions B5 and B6, the company amended CS Table 64 with the following corrections:

- Use the correct Telford et al. 2016 [31] reference (update in the CS document B) (clarification question B5)
- Anaemia disutility reference source from Telford et al. 2019 [31] to Swinburn et al. 2010.[32] Disutility and duration values remained the same (clarification question B6a).
- Disutility value and duration for dyspnoea from Telford et al. 2019 [31] instead of considering an assumption (equal to ATL increase) (duration from 28 to 12.7 days. Disutility remained the same value) (clarification question B6b)
- Hyperglycaemia disutility value instead of hypoglycaemia value from Smith-Palmer et al. 2016 [33] (from -0.122 to -0.081) (clarification question B6c)
- Thrombocytopenia disutility from -0.110 to -0.108 (clarification question B6d)

4.2.5.4 Health state utility values used in the economic model

Health state utility values in the company's base case are taken from the EMERALD trial (CS Table 65): progression-free [redacted] and post-progression [redacted]. The company report results for a scenario using a post-progression utility of 0.601 reported by Lloyd et al. (2006)[30], included as an absolute value in combination with the progression-free utility from the EMERALD trial. The company's model also includes an option to use a relative

decrement for the post-progression state, as well as pre- and post-progression from three previous NICE appraisals TA496[34], NICE TA503[35], and TA563[36].

The utilities in the model are adjusted for general population utility values, which were taken from Ara and Brazier, 2010.[37]

Disutilities were not applied in the company's base case (section 4.2.5.3). The company presented one scenario analysis with AE disutilities. These were estimated by multiplying the disutility by the frequency and duration of the AEs. The total disutility is considered only in the first model cycle.

We summarise the sources for utility parameters in Table 27.

Table 27 Summary of utility parameters used in the economic model

Parameter	Reference	Source	Comments
Health state utility	CS Table 65	EMERALD trial (data on file)	Analysis of prospective EQ-5D data taken from the trial. Lloyd et al. 2006[30] utilities were used in a scenario analysis.
Age and sex-matched general Population Utility	CS B.4.2.7.3	Ara and Brazier 2010	As per the NICE recommendation
AE disutility	CS Table 64	Literature (see CS Table 64)	Used only in scenario analysis, as the AE was considered in the regression analysis.

Source: produced by the EAG from information in the CS
Abbreviations: AE adverse event; PD progressed disease; PF progression free;

EAG conclusion on utilities

The company's approach to estimating utility values is reasonable and consistent with the NICE reference case. We report additional scenario analyses using health state utilities from previous NICE appraisals, see section 6.1.2 below.[34-36]

4.2.6 Resources and costs

4.2.6.1 Drug acquisition

The company presented the drug acquisition costs in CS B. 3.5.1.1. CS Table 66 summarises the unit drug costs.

Elacestrant is administered orally, and patients receive a 345 mg dose daily. Elacestrant is available in packages of 28 tablets (345 mg or 86 mg each tablet) with a proposed list price of [redacted] (345 mg) and [redacted] (86 mg). Elacestrant is available with a patient access scheme (PAS) prices of [redacted] (345 mg) and [redacted] (86 mg).

For each subgroup, we have different comparators:

- **Subgroup 1**: everolimus and exemestane are administered orally, and patients receive a 10 mg tablet of everolimus and 25 mg of exemestane daily. Everolimus is available in packages of 30 tablets (2.5 mg, 5 mg or 10 mg) with the lowest list price (BNF) [38] of £1,020.00 (2.5 mg), £1,912.50 (5 mg) and £2,272.05 (10 mg) per package. Exemestane is available in packages of 30 tablets (25 mg each tablet) with a list price (eMIT 2023) [39] of £4.25. The EAG observed that everolimus has lower prices in eMIT [39]: 30 tablet pack costs £403.03 (2.5 mg tablet), £471.99 (5 mg tablet), and £536.65 (10 mg tablet) than the BNF prices considered by the company.
- **Subgroup 2:** alpelisib is administered orally, and patients receive a 300 mg dose daily. Alpelisib is available in a 56-tablet package (150 mg tablet) and a 28-tablet package (200 mg tablet), both with a list price (BNF) of £4,082.14. Fulvestrant is administered via intramuscular injections of 500 mg. Patients receive the loading doses on days 1, 15 and 29 of the treatment. After that, the maintenance dose is administered monthly. Fulvestrant is available in packages with two vials of 250 mg each and a list price (eMIT 2023) [39] of £80.18 per package.

The company included relative dose intensity (RDI) adjustments for the costs of elacestrant and the comparators, see CS Table 67. The RDI estimate for elacestrant ([redacted]) is from the EMERALD trial results for subgroup 1 and the comparator estimates are from the literature: everolimus 98%, exemestrane, 100% (Jerusalem et al. 2016[40]), alpelisib and fulvestrant 94% (Alaklabi et al. 2022)[41]).

4.2.6.2 Drug administration

Costs by method of administration are shown in Table 28. Oral treatments are assumed to have no administration cost. Intramuscular injections were assumed to take 10 minutes of a primary care nurse's time, with costs from the PSSRU 2022.[42] The cost of Intravenous injections required for subsequent treatments is taken from the NHS Cost Collection 2021/22 (SB12Z: Deliver simple parenteral chemotherapy at first attendance).[43]

Table 28 Drug administration costs per method

Treatments	Method admin.	Admin. cost
Elacestrant, everolimus, exemestane, alpelisib Subsequent treatment: capecitabine	Oral	£0.00
Fulvestrant	Intra muscular	£8.67
Subsequent treatments: docetaxel, paclitaxel	IV infusion	£286.71

4.2.6.3 Health state costs

Health state costs include consultations with health and social service care professionals, hospital resource use, and treatment follow-up. The frequency of resource use was taken from the NICE TA619 (Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer)[44] manufacturer's submission, converted to the model cycle length: see CS Table 68.

Clinical advice to the EAG suggested some differences in the frequency of investigations and consultations, including less frequent GP visits and more frequent oncology specialist consultations (four appointments a year instead of two for a progression-free health state and a higher number of visits to the post-progression health state to allow treatment changes). The EAG assessed a scenario with these modifications, see section 6.1.4.

Healthcare unit costs were taken from the PSSRU 2022[42] report and NHS Cost Collection 2021/22[43] data (CS Table 69). In response to clarification question B9, the company updated the unit cost for physiotherapy in CS Table 69 from £45.50 to £48.50. With this correction, the total healthcare cost per cycle is £51.80 for the progression-free health state, and £101.12 for the progressed disease health state.

4.2.6.4 Subsequent treatment

Patients who progress to the progressed disease (PD) health state may commence chemotherapy. The unit costs for the chemotherapies that are included in the company's model (capecitabine, docetaxel, and paclitaxel) are shown in CS Table 73. The EAG notes a minor discrepancy in the list price of paclitaxel 100 mg in CS Table 73. This was corrected in response to clarification question B10 and updated in the economic model (see section 5.3.1).

CS Table 74 shows the proportion of each chemotherapy assumed in the company's base case; and the duration and treatment costs. The EAG notes discrepancies in the subsequent treatment costs in CS Table 74, which the company amended in response to clarification question B11. Table 29 below summarises the corrected subsequent treatment costs.

Table 29 Subsequent treatment costs with EAG corrections

Chemotherapy	Dose per cycle (mg)	Admin. Per cycle	Duration (cycle)	Total Drug cost (£)	Total Admin. Cost (£)	One-off cost (£)
Capecitabine	2036 mg	9.33	13.64	£110.93	£0.00	£110.93
Docetaxel	136 mg	0.33	24.00	£108.87	£2,293.68	£2,402.55
Paclitaxel	471 mg	0.33	20.90	£190.15	£1,997.41	£2,187.57

Source: Based on CS Document B Table 74 and section CS B.3.5.4.2

Based on EMERALD [17] results, the company assumed that only a proportion ([redacted]) of patients would start subsequent treatment after disease progression. The company assumed that all patients starting subsequent treatment would receive capecitabine. Therefore, the one-off cost of subsequent treatment applied on disease progression is [redacted].

Clinical advice to the EAG is that:

- Patients with slow progressing disease are most likely to be candidates for third line treatment.
- The majority of patients who have chemotherapy might receive capecitabine.
- Docetaxel would be used infrequently in this subsequent treatment setting.
- Patients receiving paclitaxel should usually receive weekly treatment with 70 to 80 mg/m^2 for 12 to 18 weeks.
- Eribulin should be considered as an option for chemotherapy.

NICE TA423[45] states that eribulin is only indicated to treat metastatic breast cancer after two or more chemotherapies. The economic model is not set up to consider multiple lines of chemotherapy. Therefore, we did not include eribulin as an additional option in the scenario analysis.

Although the company reported that subsequent treatment distributions were explored in scenario analyses, results for these scenarios were not included in the CS. We explore alternative proportions of subsequent treatments, including the proportion described in Telford et al. 2016 [31] (see section 6.1.1).

4.2.6.5 ESR1-mut testing costs

The company notes that genomic testing for ESR1 mutations is not currently funded in the NHS, but they anticipate that funding would be introduced in a similar way as for PIK3CA

mutation testing after NICE approval of alpelisib (TA816).[8] The cost of ESR1 testing in the company's model is based on the following assumptions:

- £300 per test using digital PCR (CS Table 72). In response to clarification question B8, the company reported that the digital PCR test cost was based on feedback from clinical pathologists.
- 50% of the target population will test positive for an ESR1 mutation, based on results from trials of Imlunestrant (Jhaveri et al. 2023)[46] and palazestrant (Lin et al. 2023)[47]
- 100% of patients are currently tested for the PIK3CA mutation, so no additional cost is included in the model for testing in the dual-mutation subgroup.

The company base case assumes a prevalence-based cost of £600 per person treated in their base case analysis (£300 / 50% = £600), because two people would need to be tested to identify one patient with an ESR1 mutation for whom elacestrant would be suitable.

We note that CS Table 72 also cites a prevalence-based cost of £857.46, but the basis for this estimate is unclear and it is not included in the company's model.

Clinical advice to the EAG regarding ESR1 testing is that:

- ESR1 testing in the EMERALD study was conducted with a Guardant 'liquid biopsy' assay, which uses a blood sample for circulating tumour DNA (ctDNA) analysis. Guardant360 CDx is FDA approved as a companion diagnostic for elacestrant, but an NHS price and pathway for this test is not currently available.
- The ESR1 mutation test would have to be conducted separately from current genetic testing used prior to breast cancer treatment (which identifies whether a PIK3CA mutation is present). As ESR1 is an acquired mutation that can develop after initial treatment, analysis of the primary tumour sample may not be accurate.
- ESR1 mutation testing could be conducted using the same analytical method (digital PCR based on a tissue sample) that is currently used for PIK3CA testing in the NHS, estimated to cost approximately £300.
- However, this approach has disadvantages, including either reliance on a historical tissue sample or a single site repeat biopsy, which may not reflect disease status due to tumour heterogeneity. Repeat sample collection and reporting of the result might delay the start of treatment, as the current reporting time for digital PCR is about a week. Adding ESR1 mutation testing might also burden the testing laboratories further, which could further delay the test results.

- Between 10% to 20% of patients are expected to have the dual mutation (ESR1 and PIK3CA mutations).

In response to a request from NICE, the NHS Genomic Medicine Service (GMS) provided estimates of the possible cost of ctDNA tests for ESR1 mutation in the NHS. They suggested that for the purpose of modelling the impact on the NHS, the cost of providing this testing would be in the region of [redacted]. This assumes that in the future, there would be additional targets to be tested for these patients, and that therefore the testing approach would be to use large next generation sequencing (NGS) panel testing of ctDNA samples. Currently this can be delivered by the North Thames NHS Genomic Laboratory Hub (GLH) using the Marsden360 assay at a cost of [redacted]. We understand that a number of NHS GLHs are currently exploring this or a similar delivery model for ctDNA testing. We report additional EAG scenario analysis using these GMS estimated costs, see section 6.1.5.

4.2.6.6 Adverse event costs

Adverse event costs are calculated by multiplying the total frequency of the adverse events by their unit cost. These costs are applied as a one-off in the first treatment cycle only.

The unit costs of treating each adverse event are taken from the NHS Collection Cost 2021/22[43] and are available in CS Table 70. The adverse event frequency for each treatment arm is shown in CS Table 63. The total adverse event cost for each treatment arm is shown in CS Table 71. The EAG noted some errors in CS Table 63, where adverse events frequencies were misplaced. The company corrected this table in CS document B as requested by the EAG in response to clarification question B7.

4.2.6.7 End-of-life costs

The company's model includes a cost of £8,061 for end-of-life care for deaths related to breast cancer. This estimate was taken from Round et al. 2015 [48] updated to 2021/22 prices using the NHS PSSRU cost inflation index.[42]

The PSSRU Unit Costs for Health and Social Care 2022 manual [42] reports end-of-life health and social care costs based on the Nuffield Trust report by Georghiou et al. (2012) [49], with a cost of £13,113 in the final year of life for cancer patients. The EAG ran a scenario using this source in section 6.3.

Table 30 End of life cost for health and social care

Source	Cost £ per person in the final year of life	
	Original estimate	2021/22 prices
Round et al. 2015	£7,189, 2013/14 prices	£8,061
Georghiou et al. 2012	£10,844, 2010/11 prices	£13,113

EAG comment on resources and costs

- The company's approach to estimating resources and costs in the economic model is consistent with the NICE reference case and previous technology appraisals for metastatic breast cancer.
- The EAG identified some minor errors in resource use costs (physiotherapy), subsequent treatment costs (paclitaxel 100 mg list price, total costs per treatment in CS Table 74), and adverse events (AE frequency in CS Table 63). The company corrected these errors in response to clarification questions B7, B9, B10 and B11.
- We assessed the impact of uncertainty over subsequent treatment costs in two scenarios, varying the proportions to select the most expensive treatment and the proportions in Telford et al. 2016[31]. We also tested scenarios varying the cost of ESR1 testing, healthcare resource use and the cost of end-of-life care. See section 6.1.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

CS section 3.9 Table 81 reports the base case results for elacestrant vs everolimus + exemestane (EVE + EXE) for the ESR1-mut + >12 months of prior ET + CDK4/6i population (subgroup 1) and elacestrant vs alpelisib + fulvestrant (ALP+FUL) for ESR1-mut, PIK3CA-mut+>12 months of prior ET + CDK4/6i population (subgroup 2). The company made corrections to their model in response to clarification questions and reported in an updated CS document B.

Revised deterministic base case results are reported in Table 31 below. Note that we report costs and health outcomes, including life years (LYs) and QALYs, discounted at 3.5% per year. Total and incremental QALYs are reported without the severity modifier of 1.2 applied by the company for subgroup 1 (see section 7 for further details). We report ICERs for subgroup 1 both with and without the severity modifier.

- For subgroup 1, the company's base case ICER is £24,893 per QALY gained including the severity modifier; and £29,872 per QALY gained without the severity modifier.
- For subgroup 2, the company's base case result indicates that elacestrant is dominant: with a lower expected cost and higher expected QALYs compared to alpelisib + fulvestrant. The net monetary benefit (NMB) of elacestrant is £17,803 at a cost-effectiveness threshold of £20,000 per QALY gained; and £20,570 at a threshold of £30,000 per QALY gained.

The company's base case results and all other cost-effectiveness results in this report are conducted with a proposed confidential patient access scheme (PAS) price discount for elacestrant. However, they do not include confidential discounts for any other medications. Therefore, the ICERs do not reflect the actual prices that would be paid by the NHS. Results including all available NHS price discounts for comparator and subsequent medications in addition to the proposed PAS discount for elacestrant are presented in a separate confidential addendum to this report.

Table 31 Company's base case results with PAS price for Elacestrant

Technologies	Total costs (£) [a]	Total LYG [a]	Total QALYs [a]	Incremental costs (£) [a]	Incremental LYG [a]	Incremental QALYs [a]	ICER (£/QALY) no severity modifier	ICER (£/QALY) with severity modifier (1.2)
Subgroup 1 - ESR1-mut and ≥12 months of prior ET + CDK4/6i								
Everolimus + exemestane	[redacted]	[redacted]	[redacted]					
Elacestrant	[redacted]	[redacted]	[redacted]	£18,883	0.892	0.632	£29,872	£24,893
Subgroup 2 - ESR1-mut, PIK3CA-mut and ≥12 months of prior ET + CDK4/6i								
Alpelisib + fulvestrant	[redacted]	[redacted]	[redacted]					
Elacestrant	[redacted]	[redacted]	[redacted]	-£12,269	0.394	0.277	Dominant	---

Source: CS Table 81
Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ESR1, oestrogen receptor 1 gene; ET, endocrine therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; PAS, patient access scheme; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; QALYs, quality-adjusted life years.
[a] Discounted at 3.5 % per year, with no severity modifier applied to QALYs

5.2 Company's sensitivity analyses

5.2.1 Deterministic sensitivity analyses

CS section B.3.10.2 reports the deterministic sensitivity analysis (DSA) results for elacestrant vs everolimus + exemestane (subgroup 1) and elacestrant vs alpelisib + fulvestrant (subgroup 2). The parameters varied in the DSA are listed in CS Table 79. The company notes that parametric survival model coefficients were only varied only in the PSA, not in the DSA, because these coefficients are correlated. The EAG considers that this is reasonable for testing the sensitivity of individual parameters.

The company presented two tornado diagrams based on the impact on net monetary benefit: see CS Figure 52 (elacestrant vs everolimus + exemestane for subgroup 1) and CS Figure 53 (elacestrant vs alpelisib + fulvestrant for subgroup 2). Parameters relating to the everolimus drug cost, mean age and RDI (elacestrant and everolimus) were the main drivers for the model in subgroup 1, and RDI (alpelisib and elacestrant) was the main driver in subgroup 2.

5.2.2 Scenario analysis

The company coded 59 scenarios to test structural and methodological uncertainties in its economic model (see Appendix 5 for the full list). They reported results for 20 of these scenarios in subgroup 1 (CS Table 85), and for 21 scenarios in subgroup 2 (CS Table 86):

- For subgroup 1, the ICER for elacestrant was less than £30,000 per QALY in all but one scenario: using the gamma distribution for the elacestrant OS (ICER of £43,793).
- For subgroup 2, elacestrant was dominant (positive NMB) in all scenarios.

We discuss additional scenarios of interest in section 6.1.

5.2.3 Probabilistic Sensitivity Analysis

The company's probabilistic sensitivity analysis results were estimated for 5,000 simulations, illustrated in scatterplots (CS Figures 50 and 51) and cost-effectiveness acceptability curves (CEACs, CS Figures 48 and 49).

Mean probabilistic results for the company’s base case are reported in CS Table 82). These results were revised to include corrections after the clarification response (see section 5.3.1). The probabilistic results are stable and consistent with the deterministic results.

The distributions used for the parameters included in the PSA analysis are summarised in CS Table 79:

- **Normal distribution**: patient characteristics (age, proportion female, BSA), drug unit costs (except elacestrant and alpelisib), RDI, administration costs, healthcare resource use costs, healthcare resource use frequency, subsequent treatment costs, subsequent treatment duration, ESR1-mut testing cost, adverse event costs.
- **Beta distribution**: proportion with ESR1-mut, the proportion of PFS events assumed to be in progression, adverse event frequency, and health state utility values.
- **Multinormal distribution**: OS curves (elacestrant and comparators), PFS curves (elacestrant and comparators), and general population utility coefficients (Ara and Brazier equation [37]).
- **Dirichlet**: subsequent treatment distribution

The EAG observed that all cost parameter uncertainties were represented with a normal distribution, instead of gamma or log-normal distributions. We checked the economic model and verified that all cost parameters only allow positive cost values during the PSA iterations. We also note that the subsequent treatment distribution was modelled with a Dirichlet distribution, but this was not active in the PSA.

5.3 Model validation and face validity check

We conducted a range of checks on the company's model using an EAG checklist:

- **Input checks:** comparison of all parameter values in the model against the values stated in the company submission and cited sources.
- **Output checks:** replication of results reported in the CS using the company model. Manually running scenarios and checking model outputs against results reported in the CS for the deterministic sensitivity analyses and scenario analyses.
- **'White box' checks:** checking individual equations within the model.
- **'Black box' checks:** applying a range of extreme value and logic tests to check the plausibility of changes in results when parameters are changed.

The model is generally well-implemented, although we spotted minor discrepancies between the company submission and the initial version of the model, which were corrected in a revised version submitted with the company's clarification response, as described below.

5.3.1 Company's corrections to the company model

In their response to the EAG clarification questions, the company amended some parameters values listed below:

- Mean age at baseline for the ESR1-mut and ≥12 months of prior ET + CDK4/6i (subgroup 1) (CQ B1, see section 4.2.2.1).
- Adverse events disutilities and durations in CS Table 64 (CQ B6, see section 4.2.5.3)
- Adverse event frequency in CS Table 63 (CQ B7, see section 4.2.6.6)
- Resource unit cost for physiotherapy in CS Table 69 (CQ B9, see section 4.2.6.3)
- Unit drug cost for paclitaxel 100 mg in CS Table 73 (CQ B10, see section 4.2.6.4)

The company also corrected two PSA equations (PSA sheet, column AI16:AI5015 and AJ16 to AJ5015) related to the incremental cost and QALYs, where the elacestrant total cost and total QALYs were fixed for the first iteration result values (AI$16 and AJ$16) in all 5,000 iterations. The company provided a revised model considering the clarification response modifications (version 28/05/2024).

The updated results led to a slight increase in the ICER from £24,873 to £24,893 per QALY gained for subgroup 1, including the 1.2 severity modifier. For subgroup 2, elacestrant remained dominant, with a slight increase in the NMB from £20,451 to £20,570.

5.3.2 EAG corrections to the company's model

The EAG identified a minor issue in the scenario results. In the “Scenario analysis” sheet, column BB refers to the incremental QALYs equation. This equation used the severity modifier parameter to calculate the incremental QALYs instead of a fixed value. Therefore, all scenario results change if the severity modifier parameter value is changed. In addition, this makes scenario 5 (severity modifier = 1) in row 23 or scenario 6 (severity modifier = 1.2) in row 24 incorrect, depending on the comparator. However, neither of these scenarios were reported in CS B Tables 85 and 86. We corrected only cells BB23 and BB24. This issue does not affect the base case result.

5.3.3 EAG summary of key issues and additional analyses

We summarise and critique key assumptions in the company's model in Table 32 below.

Table 32 EAG summary and critique of key features of the economic model

Aspect of model	Company assumptions	EAG comment	EAG additional analyses
Decision problem			
Population and subgroups	Target population for elacestrant restricted patients with disease progression after at least 12 months of prior ET + CDK4/6i (subgroup 1). Results also presented for the dual mutated subgroup within the target population (subgroup 2).	Results are based on post-hoc analysis of EMERALD trial data by duration of prior therapy. This improves the estimated cost-effectiveness of elacestrant but increases uncertainty due to the smaller sample sizes.	None
Mean age at baseline	Base case from EMERALD trial. Scenario Flatiron means (CQ response Table 5)	The scenario with Flatiron mean ages is consistent with the use of MAIC-adjusted clinical outcomes in the model	EAG preferred: Flatiron Scenario: EMERALD
Comparators	Everolimus + exemestane for subgroup 1 Alpelisib + fulvestrant for subgroup 2	This is reasonable, although ET with or without chemotherapy, or chemotherapy alone may be used for some patients	None
Clinical effectiveness			
Survival extrapolations	Independent curves fitted to MAIC-weighted EMERALD data and Flatiron KM	Uncertainty due to unanchored MAIC and small sample sizes	Additional scenarios, see Table 33 and Table 34 below
OS distribution	Subgroup 1: log-logistic for elacestrant; gamma for everolimus + exemestane	Subgroup 1 base case predicts long-term OS benefit for elacestrant which is	EAG preferred:

Aspect of model	Company assumptions	EAG comment	EAG additional analyses
	Subgroup 2: Weibull for elacestrant; gamma for alpelisib + fulvestrant	optimistic given current evidence. Agree with base case for subgroup 2	Subgroup 1: gamma both arms Subgroup 2: No change Additional scenarios
PFS distribution	Subgroup 1: log-normal for both arms Subgroup 2: log-normal for both arms	Agree	Additional scenarios
Treatment duration	KM from EMERALD trial for elacestrant Assume TTD = PFS for comparator arms	Agree with use of KM for elacestrant. But potential bias against comparators if some patients discontinue prior to disease progression	Exploratory scenarios with adjustment of comparator TTD relative to the PFS
Health-related quality of life			
Health state utilities	Estimates from the EMERALD trial, mapped from EQ-5D-5L to EQ-5D-3L (CS Table 65)	We agree	Additional scenarios with utilities from previous NICE appraisals [34-36]
Adverse event disutilities	AE disutility and duration presented in CS Table 64. Utility regression includes AE term, so additional AE disutility was not included in the company's base case	We agree	No change
Age-related utility decrement	Adjustment from Ara and Brazier 2010 [37]	We agree	No change

Aspect of model	Company assumptions	EAG comment	EAG additional analyses
Resource use and costs			
Treatment cost	CS B.3.5.1.1 and Table 66. Everolimus and alpelisib were sourced from BNF 2024 and exemestane and fulvestrant from eMIT 2023	The eMIT tool presented a lower acquisition price for everolimus.	EAG preferred: everolimus price from eMIT
Relative dose intensity (RDI)	CS B.3.5.1.1 and Table 67. Parameters were collected from the EMERALD trial for elacestrant and from the literature for the comparators.	We agree	No change
Administration cost	CS B.3.5.1.2 and Table	We agree	No change
Resource use and costs	Based on NICE TA619[44] and presented in CS Table 68.	We agree	Additional scenario based on clinical advice regarding resource use frequency (see Table in section 0).
Subsequent treatments	The proportions of patients receiving chemotherapies were based on assumptions.	Uncertainty over % use of each chemotherapy for progressed disease health state.	Additional scenarios for distribution of subsequent treatments (see Table 29 in section 6.1.1).
ESR1 mutation testing	Cost based on digital PCR testing (~£300). Prevalence-based cost £600 per person treated, assuming 50% of tested have ESR1-	There is uncertainty over the cost of introducing ESR1 testing in the NHS. Potential service implications due to the	Exploratory scenarios varying for ESR1 test cost and

Aspect of model	Company assumptions	EAG comment	EAG additional analyses
	mut (£300 / 50%). Potential for introduction of liquid-based biopsy as companion diagnostic.	delay of results for digital PCR, and pressure on genomic testing facilities	number needed to test to find one positive (see section 6.1).
Adverse event	Costs in CS Table 70 based on NHS Cost Collection 2021/22[43]. AE frequency is in CS Table 63 with estimates from the literature.	We agree	No change
End-of-life	Based on estimates from Round et al. 2015[48]	We agree	Additional scenario with Georghiou et al. 2012[49] cost (see Table 30 in section 4.2.6.7)

6 EAG'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

Based on the EAG critique of the company's model assumptions (Table 32), we performed a range of additional scenario analyses, which are summarised in the following subsections.

6.1.1 Exploratory scenarios: survival curves (OS, PFS and TTD)

See section 4.2.4 above for EAG discussion and conclusions on the selection of survival curves for OS, PFS and TTD. We summarise the company's base case and scenarios and EAG additional scenarios for subgroup 1 and 2 in Table 33 and Table 34 respectively.

Table 33 Survival analysis – scenario analysis (subgroup 1)

	Elacestrant	**Everolimus + exemestane**
OS		
Company base case	Log-logistic	Gamma
Company scenarios	Gamma, Log-normal	Weibull, exponential
EAG scenarios	Weibull	+ MAIC HR
	Gamma	+ MAIC HR
	Generalised gamma	+ MAIC HR
	Log-logistic	+ MAIC HR
PFS		
Company base case	Log-normal	Log-normal
Company scenarios	Log-logistic	log-logistic, gamma
EAG scenarios	Exponential	
		Weibull
TTD		
Company base case	KM curve	Assumed equal to PFS
Company scenarios	log-normal, log-logistic	
EAG scenarios	Generalised gamma	
		HR of 0.8 for TTD versus PFS

Table 34 Survival analysis – scenario analysis (subgroup 2)

	Elacestrant	**Alpelisib + fulvestrant**
OS		
Company base case	Weibull	Gamma
Company scenarios	Gamma, log-normal	Weibull, log-normal

	Elacestrant	Alpelisib + fulvestrant
EAG scenarios	Gompertz	+ MAIC HR
	Weibull	+ MAIC HR
	Gamma	+ MAIC HR
PFS		
Company base case	Log-normal	Log-normal
Company scenarios	Log-logistic, exponential	Generalised gamma, gamma
EAG scenarios		Weibull
TTD		
Company base case	KM curve	Equal to PFS
Company scenarios	Log-normal, log-logistic	
EAG scenarios		HR of 0.5 for TTD versus PFS

6.1.1.1 EAG survival scenario results for subgroup 1

The EAG exploratory scenarios for survival curves in subgroup 1 had the following results (company base case: ICER £24,893 per QALY, with the 1.2 QALY weight).

For the OS curves, we tested the following distributions for elacestrant with the MAIC hazard ratio used to estimate curves for the comparator EVE + EXE:

- Weibull distribution: ICER £44,266 per QALY
- Gamma distribution: ICER £36,925 per QALY
- Generalised Gamma: ICER £51,802 per QALY
- Log-logistic distribution: ICER £27,070 per QALY

For the PFS curves (independently fitted curves as in the company's base case):

- Exponential for elacestrant PFS: ICER £25,174 per QALY
- Weibull for the EVE + EXE PFS: ICER £25,627 per QALY

For the TTD curves:

- Generalised gamma for elacestrant TTD: ICER £30,457 per QALY
- HR of 0.8 for EVE + EXE TTD vs PFS: ICER £27,782 per QALY

6.1.1.2 EAG survival scenario results for subgroup 2

The EAG exploratory scenario for survival curves in subgroup 2 had the following results (company base case: elacestrant dominant, NMB £20,570 at £30,000 per QALY threshold).

For the OS curves, we tested the following distributions for elacestrant with the MAIC hazard ratio used to estimate curves for the ALP + FUL comparator:

- Gompertz: elacestrant dominant, NMB £16,697 at £30,000 per QALY threshold
- Weibull: elacestrant dominant, NMB £19,341 at £30,000 per QALY threshold
- Gamma: elacestrant dominant, NMB £21,438 at £30,000 per QALY threshold

With the EAG scenario using an independent Weibull distribution for the ALP+FUL PFS curve, elacestrant remained dominant, with an NMB £20,737 at the £30,000 per QALY threshold.

The EAG scenario with ALP+FUL TTD estimated assuming a 0.5 hazard ratio relative to the ALP+FUL PFS curve resulted in an ICER of £4,362 per QALY (elacestrant not dominant).

6.1.2 Exploratory scenarios: utilities

The company reported one scenario for health state utilities (pre- and post-progression) using values from Lloyd et al. (2006).[30] We considered additional scenarios that were included in the model but not reported in the CS, with health state utilities taken from previous NICE appraisals of untreated advanced HR+ breast cancer:

- NICE TA496 (ribociclib)[34], based on MONALEESA-2 trial data;
- NICE TA503 (fulvestrant)[35] based on FALCON trial data; and
- NICE TA563 (abemaciclib)[36], based on MONARCH 3 trial data.

Table 35 Utility values – scenario analysis

Health state	EMERALD	NICE TA496	NICE TA503 [a]	NICE TA563	Lloyd et al. 2006
PFS on treatment	[redacted]	0.774	0.751	0.690	0.715
PFS off treatment	[redacted]	0.774	0.751	0.690	0.715
Post-progression	[redacted]	0.505	0.691	0.505	0.600
Progression decrement	[redacted]	0.269	0.060	0.185	0.115

Source: Partly reproduced from CS Table 65 and economic model
[a] Telford et al. 2019[31] also based their utilities on the FALCON trial, so their utilities are equal to NICE TA503

For subgroup 1, the ICER varied between £24,968 (NICE TA503) to £28,958 (NICE TA563) including the QALY weight of 1.2. The scenarios with NICE TA496 and Lloyd et al. 2006 health state utilities had an ICER of £26,547 and £26,937, respectively.

For subgroup 2, elacestrant remained dominant for all utility scenarios. The NMB varied between £18,497 (NICE TA563) and £20,425 (NICE TA503) for a WTP of over £30,000 (base case NMB £20,570). The scenarios with Lloyd et al. 2006 and NICE TA496 health state utilities had an NMB of £19,603 and £18,658 for a WTP of over £30,000, respectively.

6.1.3 Exploratory scenarios: subsequent treatment distribution

To address the observations in section 4.2.6.4 about the distribution of subsequent treatments, we explored two scenarios, including the distribution in Telford et al. 2019[31] for second-line treatment and a scenario with a more expensive treatment (see Table 36 below). Although the subsequent treatment costs increased in these scenarios, the difference between arms was very small (see Table 37).

Table 36 Subsequent treatment distribution

Chemotherapy	Company submission	EAG scenario 1 - Telford et al. 2019 (2nd line treatment)[a]	EAG scenario 2
Capecitabine	100%	48%	0%
Docetaxel	0%	28%	0%
Paclitaxel	0%	24%	100%

Table 37 EAG scenarios: Subsequent treatment costs variation

Scenario	Subsequent treatment costs		Difference between arms
	Elacestrant	Comparator	
Subgroup 1 – elacestrant vs everolimus + exemestane			
Company base case	[redacted]	[redacted]	-£2
EAG scenario 1	[redacted]	[redacted]	-£21
EAG scenario 2	[redacted]	[redacted]	-37
Subgroup 2 – elacestrant vs alpelisib + fulvestrant			
Company base case	[redacted]	[redacted]	-£1
EAG scenario 1	[redacted]	[redacted]	-£3
EAG scenario 2	[redacted]	[redacted]	-£4

Source: produced by the EAG from the company's model

6.1.4 Exploratory scenario: resource use

As per clinical advice (section 4.2.6.3), the EAG explored a scenario adjusting the number of visits to the GP and specialist oncologist, as shown in Table 38 below. For subgroup 1, this scenario increased the ICER by £231. For subgroup 2, the resource use cost increment was £191, and elacestrant remained dominant.

Table 38 Healthcare resource use (frequency per month) – scenario analysis

Resource	Company base case		EAG scenario	
	Progression free	Post progression	Progression free	Post progression
GP visit	1.00	1.50	0.25	0.38
Oncology specialist	0.17	0.50	0.33	1.00

Source: Partly reproduced from CS Document B Table 68

6.1.5 Exploratory scenario: ESR1 mutation test

The EAG conducted four exploratory scenarios to assess the impact of uncertainty over the cost of ESR1 mutation testing. The scenarios are summarised in Table 39 below.

Table 39 ESR1 mutation test costs – scenario analysis

Scenario	Source	Non prevalence based cost	Prevalence based cost [a]
Company base case	Digital PCR	£300	£300/0.5 = £600
Company scenario	Exclude ESR1 mutation testing cost		
EAG scenarios	Estimated NHS GMS	[redacted]	[redacted] /0.5 = [redacted]
	Marsden360 assay	[redacted]	[redacted] /0.5 = [redacted]

Source: Produced by the EAG using information from the CS and GMS estimates
[a] Assuming 50% prevalence of ESR1 mutation at the point of testing

For subgroup 1 (QALY weight of 1.2 applied):

- Non-prevalence based
  - NHS GMS estimate: ICER £25,223 per QALY.
  - Marsden360 assay: ICER £26,343 per QALY
- Prevalence-based
  - NHS GMS estimate: ICER £26,343 per QALY.
  - Marsden360 assay: ICER £28,585 per QALY

For subgroup 2, elacestrant is dominant for all scenarios and:

- Non-prevalence based
  - NHS GMS estimate: NMB £20,320 at £30,000 per QALY threshold
  - Marsden360 assay: NMB £19,470 at £30,000 per QALY threshold
- Prevalence-based
  - NHS GMS estimate: NMB £19,470 at £30,000 per QALY threshold
  - Marsden360 assay: NMB £17,770 at £30,000 per QALY threshold

6.2 EAG's preferred assumptions

Based on the EAG critique of the company's model discussed in Table 32, we have identified four key aspects of the company base case with which we disagree. Our preferred model assumptions are the following:

- Mean age from the Flatiron database (see section 4.2.2.1)
- Everolimus prices from eMIT 2023 instead of the BNF (see section 4.2.6.1). This only affects subgroup 1.
- The proportion of positive ESR1 tests for subgroup 2 (dual mutated) based on clinical advice estimate of 20% (see section 4.2.6.5). The proportion of positive cases for subgroup 1 remains at 50%.
- OS extrapolations: subgroup 1 independent gamma for both arms
  (no change to company base case for subgroup 2)

Table 40 shows the cumulative cost-effectiveness results for subgroup 1 of adding the EAG's preferred model assumptions one at a time to the corrected company's base case. Including all of the EAG's preferred assumptions increases the ICER from £24,893 to £73,224 per QALY (including the QALY weight of 1.2).

Table 40 EAG's preferred assumptions: cumulative change to ICER for subgroup 1

Preferred assumption	Treatment	Total costs	Total QALYs	ICER £/QALY No QALY weight	ICER £/QALY With QALY weight
Company's revised base case	EVE + EXE	[redacted]	[redacted]	£29,872	£24,893
	Elacestrant	[redacted]	[redacted]		
+ Mean age from Flatiron ([redacted] yrs)	EVE + EXE	[redacted]	[redacted]	£29,942	£24,952
	Elacestrant	[redacted]	[redacted]		
	EVE + EXE	[redacted]	[redacted]	£47,723	£39,769

Preferred assumption	Treatment	Total costs	Total QALYs	ICER £/QALY No QALY weight	ICER £/QALY With QALY weight
+ Everolimus price from eMIT 2023	Elacestrant	[redacted]	[redacted]		
+ OS Independent gamma both arms	EVE + EXE	[redacted]	[redacted]	£87,869	£73,224
	Elacestrant	[redacted]	[redacted]		
EAG base case	EVE + EXE	[redacted]	[redacted]	£87,869	£73,224
	Elacestrant	[redacted]	[redacted]		

Source: Produced by the EAG from the company's model

Table 41 shows the cumulative cost-effectiveness results of adding the EAG's preferred model assumptions for subgroup 2. Elacestrant remains dominant, with a small reduction in the NMB from £20,570 to £19,670 at the £30,000 per QALY threshold.

Table 41 EAG's preferred assumptions: cumulative change to ICER for subgroup 2

Preferred assumption	Treatment	Total Costs	Total QALYs	ICER £/QALY	NMB (£) at WTP £30,000
Company's revised base case	ALP + FUL	[redacted]	[redacted]	Dominant	£20,570
	Elacestrant	[redacted]	[redacted]		
+ Mean age from Flatiron ([redacted] yrs)	ALP + FUL	[redacted]	[redacted]	Dominant	£20,570
	Elacestrant	[redacted]	[redacted]		
+ Proportion of positive ESR1-mut tests (20%)	ALP + FUL	[redacted]	[redacted]	Dominant	£19,670
	Elacestrant	[redacted]	[redacted]		
EAG base case	ALP + FUL	[redacted]	[redacted]	Dominant	£19,670
	Elacestrant	[redacted]	[redacted]		

Source: Produced by the EAG from the company's model

We confirmed that the severity modifier QALY weight is unchanged (1.2 for subgroup 1 and no weight for subgroup 2), see section 7.2.

We reran the probabilistic sensitivity analysis (PSA) with the EAG base case model. The cost-effectiveness scatterplot is shown in Figure 9 (subgroup 1) and Figure 10 (subgroup 2). The probabilistic results are aligned with the deterministic results (see Table 42), with a 3% difference in the ICER for subgroup 1 and a 0.7% difference in NMB (£19,808 for a WTP of £30,000) for subgroup 2.

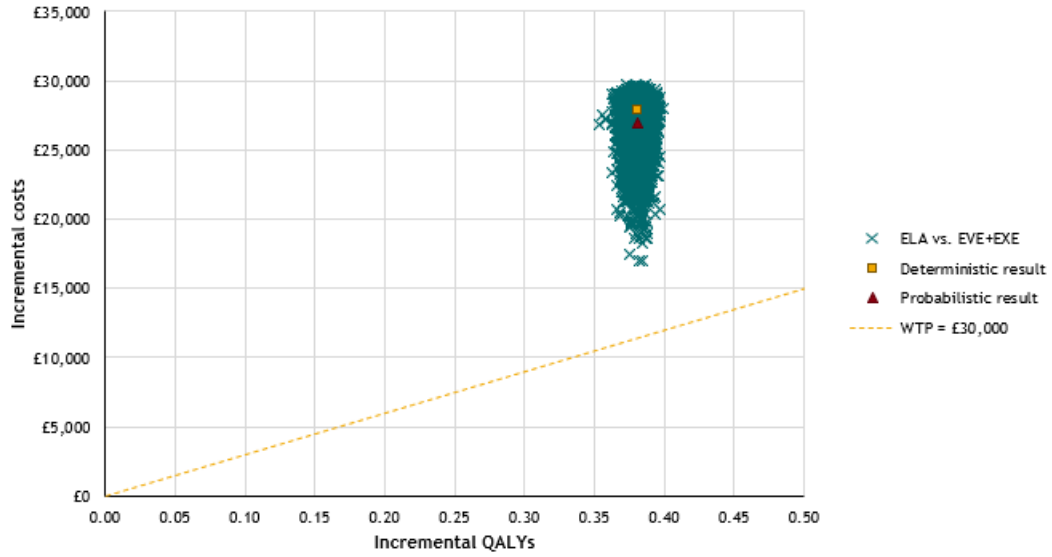

Figure 9 PSA scatterplot graph for subgroup 1 using the EAG preferred assumptions

PSA: probabilistic sensitivity analysis, QALY Quality-adjusted life year, WTP: willingness to pay, ELA: elacestrant, EVE + EXE: everolimus with exemestane

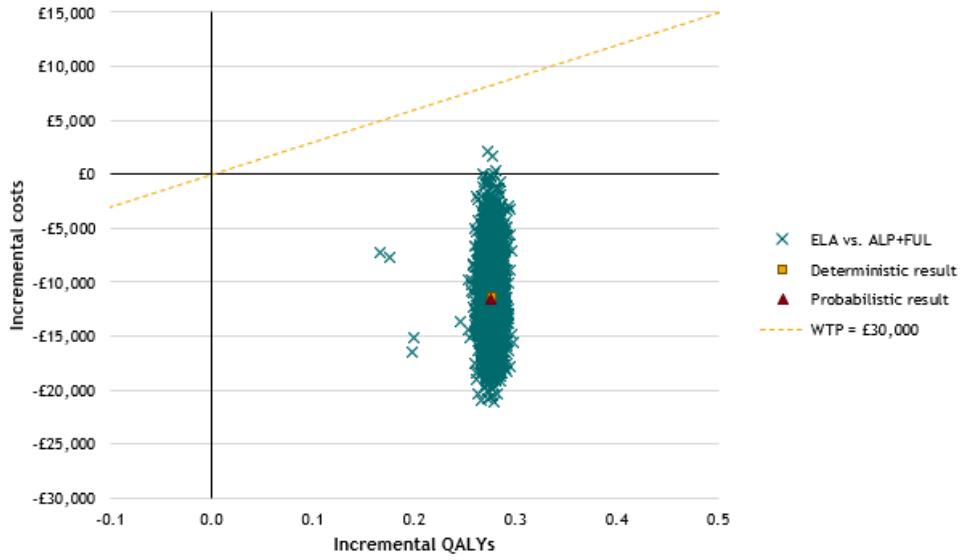

Figure 10 PSA scatterplot graph for subgroup 2 using the EAG preferred assumptions

PSA: probabilistic sensitivity analysis, QALY Quality-adjusted life year, WTP: willingness to pay, ELA: elacestrant, ALP + FUL: alpelisib with fulvestrant

Table 42 Probabilistic sensitivity analysis results – EAG base case

Technologies	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY) no severity modifier	ICER (£/QALY) with severity modifier 1.2
Subgroup 1 - ESR1-mut and ≥12 months of prior ET + CDK4/6i								
EVE + EXE	[redacted]	[redacted]	[redacted]					
Elacestrant	[redacted]	[redacted]	[redacted]	£26,953	0.422	0.317	£84,914	£70,762
Subgroup 2 - ESR1-mut, PIK3CA-mut and ≥12 months of prior ET + CDK4/6i								
ALP + FUL	[redacted]	[redacted]	[redacted]				Dominant	Not applicable
Elacestrant	[redacted]	[redacted]	[redacted]	-£11,522	0.393	0.276		

Source: Produced by the EAG from the company's economic model

6.3 Scenario analyses conducted with the EAG's preferred assumptions

We performed a range of scenario analyses with the EAG base case to analyse the impact of changing some of the model assumptions. The scenarios in Table 43 and Table 44 are divided into four groups:

- Company base case assumptions that were modified in the EAG preferred analysis (section 6.1)
- Selection of relevant company scenarios described in section 5.2.2
- Selection of relevant additional company scenarios described in Appendix 9.5
- Selection of relevant EAG exploratory scenarios described in section 6.1

6.3.1 Subgroup 1

Table 43 below summarises the results of the scenarios on the EAG base case for subgroup 1. The ICER varied from £35,240 (elacestrant OS – log-normal) to £262,288 (elacestrant OS - Gompertz), assuming a 1.2 QALY weight.

The scenarios that have the most significant effect on the cost-effectiveness are:

- Changes to the elacestrant OS distribution. All five scenarios varied the ICER by more than 45%:
  - The log-normal, exponential and log-logistic distributions decreased the ICER to £35,240, £35,966, and £39,769, respectively.
  - The Weibull and Gompertz distributions increased the ICER to £107,211 and £262,288, respectively.
- Taking the everolimus price from the BNF 2024, instead of eMIT 2023, reduced the ICER by £29,416 (40% decrease).
- Using MAIC hazard ratios, instead of independent parametric survival extrapolations, decreased the ICER by £9,641
- Assuming extrapolation curves for the elacestrant TTD (instead of the KM curve) decreased the ICER by £4,537 using the log-normal distribution and by £5,929 using the log-logistic distribution.
- Varying the ESR1 mutation test cost, with or without adjustment for prevalence, varied the ICER from £73,880 (< 1% increase) to £80,573 (10% increase).

Table 43 EAG scenario analyses for subgroup 1

EAG base case	Scenario	Treatment	Total cost (£)	Total QALYs	ICER (£/QALY) without the severity modifier	ICER (£/QALY) with the 1.2 severity modifier
EAG base case		EVE + EXE	[redacted]	[redacted]	£87,869	£73,224
		Elacestrant	[redacted]	[redacted]		
Company base case assumptions						
Mean age from Flatiron	Mean age from EMERALD	EVE + EXE	[redacted]	[redacted]	£87,838	£73,198
		Elacestrant	[redacted]	[redacted]		
Everolimus price from eMIT 2023	Everolimus price from BNF 2024	EVE + EXE	[redacted]	[redacted]	£52,570	£43,808
		Elacestrant	[redacted]	[redacted]		
Independent gamma for OS curve - both arms	Elacestrant OS – log-logistic	EVE + EXE	[redacted]	[redacted]	£47,723	£39,769
		Elacestrant	[redacted]	[redacted]		
Selected scenarios presented in the submission						
MAIC approach – independent PSM extrapolation	HR	EVE + EXE	[redacted]	[redacted]	£76,300	£63,583
		Elacestrant	[redacted]	[redacted]		
Elacestrant OS – gamma distribution	Log-normal	EVE + EXE	[redacted]	[redacted]	£42,288	£35,240
		Elacestrant	[redacted]	[redacted]		
EVE + EXE OS – Gamma distribution	Weibull	EVE + EXE	[redacted]	[redacted]	£89,199	£74,332
		Elacestrant	[redacted]	[redacted]		

EAG base case	Scenario	Treatment	Total cost (£)	Total QALYs	ICER (£/QALY) without the severity modifier	ICER (£/QALY) with the 1.2 severity modifier
	Exponential	EVE + EXE	[redacted]	[redacted]	£99,295	£82,746
		Elacestrant	[redacted]	[redacted]		
Elacestrant PFS – log-normal distribution	Log-logistic	EVE + EXE	[redacted]	[redacted]	£87,845	£73,204
		Elacestrant	[redacted]	[redacted]		
EVE + EXE PFS – log-normal distribution	Log-logistic	EVE + EXE	[redacted]	[redacted]	£87,838	£73,198
		Elacestrant	[redacted]	[redacted]		
	Gamma	EVE + EXE	[redacted]	[redacted]	£87,935	£73,279
		Elacestrant	[redacted]	[redacted]		
Elacestrant TTD – KM curve	Log-normal	EVE + EXE	[redacted]	[redacted]	£82,424	£68,687
		Elacestrant	[redacted]	[redacted]		
	Log-logistic	EVE + EXE	[redacted]	[redacted]	£80,754	£67,295
		Elacestrant	[redacted]	[redacted]		
Progressed utility source – EMERALD EQ-5D analysis ([redacted])	Lloyd et al. (2006), absolute approach (0.601)	EVE + EXE	[redacted]	[redacted]	£84,919	£70,766
		Elacestrant	[redacted]	[redacted]		
Company's additional scenario analysis presented in the economic model						
Elacestrant OS: Gamma	Weibull	EVE + EXE	[redacted]	[redacted]	£128,654	£107,211
		Elacestrant	[redacted]	[redacted]		

EAG base case	Scenario	Treatment	Total cost (£)	Total QALYs	ICER (£/QALY) without the severity modifier	ICER (£/QALY) with the 1.2 severity modifier
	Gompertz	EVE + EXE	[redacted]	[redacted]	£314,746	£262,288
		Elacestrant	[redacted]	[redacted]		
	Exponential	EVE + EXE	[redacted]	[redacted]	£43,159	£35,966
		Elacestrant	[redacted]	[redacted]		
EVE+EXE PFS: log-normal	Weibull	EVE + EXE	[redacted]	[redacted]	£87,931	£73,276
		Elacestrant	[redacted]	[redacted]		
Elacestrant TTD: KM curve	generalised gamma	EVE + EXE	[redacted]	[redacted]	£94,411	£78,676
		Elacestrant	[redacted]	[redacted]		
EAG exploratory scenarios						
EVE + EXE TTD: equal to PFS	HR for TTD vs. PFS = 0.8	EVE + EXE	[redacted]	[redacted]	£89,509	£74,591
		Elacestrant	[redacted]	[redacted]		
Subsequent treatment cost: 100% capecitabine	Scenario 1 (Telford et. al. 2019) (section 6.1.3)	EVE + EXE	[redacted]	[redacted]	£87,815	£73,179
		Elacestrant	[redacted]	[redacted]		
ESR1-mut testing cost: £300, prevalence based (50%) = £600	NHS GMS, prevalence-based: [redacted] /0.5= [redacted]	EVE + EXE	[redacted]	[redacted]	£91,333	£76,111
		Elacestrant	[redacted]	[redacted]		
	NHS GMS, non-prevalence base: [redacted]	EVE + EXE	[redacted]	[redacted]	£88,656	£73,880
		Elacestrant	[redacted]	[redacted]		

EAG base case	Scenario	Treatment	Total cost (£)	Total QALYs	ICER (£/QALY) without the severity modifier	ICER (£/QALY) with the 1.2 severity modifier
	Marsden360 assay cost, prevalence-based: [redacted] /0.5 = [redacted]	EVE + EXE	[redacted]	[redacted]	£96,688	£80,573
		Elacestrant	[redacted]	[redacted]		
	Marsden 360 assay, non-prevalence base: [redacted]	EVE + EXE	[redacted]	[redacted]	£91,333	£76,111
		Elacestrant	[redacted]	[redacted]		
ESR1-mut testing – proportion of positive tests (50%)	25%	EVE + EXE	[redacted]	[redacted]	£89,759	£74,799
		Elacestrant	[redacted]	[redacted]		
End of life cost: Round et al. 2015	Georghiou et al. 2012	EVE + EXE	[redacted]	[redacted]	£87,638	£73,031
		Elacestrant	[redacted]	[redacted]		
Utilities (PF and PD) from EMERALD EQ-5D analysis	Utilities From Lloyd et al. 2006 (PF and PFD)	EVE + EXE	[redacted]	[redacted]	£89,547	£74,622
		Elacestrant	[redacted]	[redacted]		

Source: Produced by the EAG from the company's model

6.3.2 Subgroup 2

Table 44 below summarises the results of the scenarios on the EAG base case for subgroup 2. The NMB varied from £9 (ALP+FUL TTD: HR for TTD vs. PFS = 0.2775) to £37,469 (elacestrant OS – log-normal). Elacestrant remained dominant in all scenarios, except when we assumed a hazard ratio for ALP+FUL TTD vs. ALP+FUL PFS of less than 0.6. Fourteen of 24 scenarios varied the ICER by more than 5%.

The scenarios that have the biggest effects on the cost-effectiveness are:

- The results for subgroup 2 are sensitive to assumptions regarding the comparator TTD. We examined this by varying the ALP+FUL TTD relative to the ALP+FUL PFS using an assumed hazard ratio (HR). Elacestrant remains dominant with an assumed HR between 0.6 and 1. Elacestrant is not dominant but has an ICER below £30,000 per QALY with an HR is between 0.2775 and 0.5785. And elacestrant has an ICER above £30,000 per QALY threshold with an HR of less than 0.2775. We estimate the HR at which the mean TTD for elacestrant and ALP+FUL are similar at approximately 0.46, which yields an ICER of £11,519 per QALY.
- Assuming Gamma or log-normal distributions for elacestrant OS increases the NMB by £4,952 and £17,799, respectively.
- Assuming a Weibull distribution for the ALP + FUL OS increases the NMB by £1,372. Whereas a log-normal ALP + FUL OS decreases the NMB by £5,132.
- Assuming a log-normal distribution for elacestrant TTD instead of the KM curve increases the NMB by £2,730, and the log-logistic distribution increases the NMB by £5,455.
- Elacestrant remained dominant for all ESR1 mutation test scenarios. Varying the ESR1-mut testing cost inversely affects the NMB. Increasing the total cost by £7,000 (Marsden assay cost, prevalence-based) decreases the NMB by £7,000. The NMB varied from £12,670 to £20,320.

Table 44 EAG scenario analyses for subgroup 2

EAG base case	Scenario	Treatment	Total cost (£)	Total QALYs	ICER (£/QALY) without the severity modifier	Net monetary benefit (£) at £30,000 per QALY gained
EAG base case		ALP + FUL	[redacted]	[redacted]	Dominant	£19,670
		Elacestrant	[redacted]	[redacted]		
Company base case assumptions						
Mean age from Flatiron	Mean age from EMERALD	ALP + FUL	[redacted]	[redacted]	Dominant	£19,670
		Elacestrant	[redacted]	[redacted]		
Proportion of positive cases after ESR1-mut testing (20%)	Proportion of positive cases after ESR1-mut testing (50%)	ALP + FUL	[redacted]	[redacted]	Dominant	£20,570
		Elacestrant	[redacted]	[redacted]		
Company scenarios presented in the submission						
MAIC approach – independent PSM extrapolation	HR	ALP + FUL	[redacted]	[redacted]	Dominant	£18,441
		Elacestrant	[redacted]	[redacted]		
Elacestrant OS - Weibull	Gamma	ALP + FUL	[redacted]	[redacted]	Dominant	£24,622
		Elacestrant	[redacted]	[redacted]		
	Log-normal	ALP + FUL	[redacted]	[redacted]	Dominant	£37,469
		Elacestrant	[redacted]	[redacted]		

EAG base case	Scenario	Treatment	Total cost (£)	Total QALYs	ICER (£/QALY) without the severity modifier	Net monetary benefit (£) at £30,000 per QALY gained
ALP+FUL OS - Gamma	Weibull	ALP + FUL	[redacted]	[redacted]	Dominant	£21,042
		Elacestrant	[redacted]	[redacted]		
	Log-normal	ALP + FUL	[redacted]	[redacted]	Dominant	£14,538
		Elacestrant	[redacted]	[redacted]		
Elacestrant PFS – log-normal	Log-logistic	ALP + FUL	[redacted]	[redacted]	Dominant	£19,634
		Elacestrant	[redacted]	[redacted]		
	Exponential	ALP + FUL	[redacted]	[redacted]	Dominant	£20,070
		Elacestrant	[redacted]	[redacted]		
ALP+FUL PFS – log-normal	Generalised gamma	ALP + FUL	[redacted]	[redacted]	Dominant	£21,266
		Elacestrant	[redacted]	[redacted]		
	Gamma	ALP + FUL	[redacted]	[redacted]	Dominant	£19,390
		Elacestrant	[redacted]	[redacted]		
Elacestrant TTD – KM curve	Log-normal	ALP + FUL	[redacted]	[redacted]	Dominant	£22,400
		Elacestrant	[redacted]	[redacted]		
	Log-logistic	ALP + FUL	[redacted]	[redacted]	Dominant	£25,125
		Elacestrant	[redacted]	[redacted]		
Progressed utility source – EMERALD EQ-5D ([redacted])	Lloyd et al. 2006 absolute approach	ALP + FUL	[redacted]	[redacted]	Dominant	£18,767
		Elacestrant	[redacted]	[redacted]		

EAG base case	Scenario	Treatment	Total cost (£)	Total QALYs	ICER (£/QALY) without the severity modifier	Net monetary benefit (£) at £30,000 per QALY gained
Company additional scenarios presented in the economic model						
ALP+FUL PFS – log-normal	Weibull	ALP + FUL	[redacted]	[redacted]	Dominant	£19,837
		Elacestrant	[redacted]	[redacted]		
EAG additional scenarios						
ALP + FUL TTD: equal to PFS	HR for TTD vs. PFS = 0.2775	ALP + FUL	[redacted]	[redacted]	£29,969	£9
		Elacestrant	[redacted]	[redacted]		
	HR for TTD vs. PFS = 0.46	ALP + FUL	[redacted]	[redacted]	£11,519	£5,114
		Elacestrant	[redacted]	[redacted]		
	HR for TTD vs. PFS = 0.5785	ALP + FUL	[redacted]	[redacted]	£9	£8,299
		Elacestrant	[redacted]	[redacted]		
	HR for TTD vs. PFS = 0.6	ALP + FUL	[redacted]	[redacted]	Dominant	£8,873
		Elacestrant	[redacted]	[redacted]		
Subsequent treatment cost: 100% capecitabine	Telford et al. 2019 (section 6.1.3)	ALP + FUL	[redacted]	[redacted]	Dominant	£19,672
		Elacestrant	[redacted]	[redacted]		
ESR1-mut testing cost: £300, prevalence-based (20%)=£1,500	NHS GMS, prevalence-based: [redacted] /0.2= [redacted]	ALP + FUL	[redacted]	[redacted]	Dominant	£16,920
		Elacestrant	[redacted]	[redacted]		
	NHS GMS, non-prevalence base: [redacted]	ALP + FUL	[redacted]	[redacted]	Dominant	£20,320
		Elacestrant	[redacted]	[redacted]		

EAG base case	Scenario	Treatment	Total cost (£)	Total QALYs	ICER (£/QALY) without the severity modifier	Net monetary benefit (£) at £30,000 per QALY gained
	Marsden360 assay cost, prevalence-based: [redacted] /0.2 = [redacted]	ALP + FUL	[redacted]	[redacted]	Dominant	£12,670
		Elacestrant	[redacted]	[redacted]		
	Marsden360 assay, non-prevalence base: [redacted]	ALP + FUL	[redacted]	[redacted]	Dominant	£19,470
		Elacestrant	[redacted]	[redacted]		
ESR1-mut testing – 20% of positive tests	10%	ALP + FUL	[redacted]	[redacted]	Dominant	£18,170
		Elacestrant	[redacted]	[redacted]		
End of life cost: Round et al. 2015	Georghiou et al. 2012	ALP + FUL	[redacted]	[redacted]	Dominant	£19,738
		Elacestrant	[redacted]	[redacted]		
Utilities (PF and PD) from EMERALD EQ-5D analysis	Utilities from Lloyd et al. 2006	ALP + FUL	[redacted]	[redacted]	Dominant	£18,706
		Elacestrant	[redacted]	[redacted]		

Source: Produced by the EAG from the company's model

6.4 Conclusions on the cost-effectiveness evidence

The EAG identified a set of assumptions and input parameter values that we prefer to those used in the company's base case analysis. See Table 32 for description and justification for these assumptions.

For subgroup 1, the EAG's preferred assumptions increased the ICER for elacestrant versus everolimus with exemestane from £24,893 to £73,224 per QALY (including a severity modifier of 1.2). The results are most sensitive to changes in the overall survival curve for elacestrant, the everolimus price, and using the MAIC hazard ratio approach, instead of independent parametric distributions for the survival curves.

For subgroup 2, elacestrant remained dominant with the EAG's preferred assumptions, with an NMB of £19,670 at the £30,000 per QALY threshold (no severity modifier is applicable for subgroup 2). The results are most sensitive to changes in the ALP+FUL TTD assumption (assumed equal to the PFS curve in the base case and varied relative to the PFS in EAG scenario analysis), the elacestrant OS and ALP+FUL OS distributions, as well as the ESR1-mut testing cost and proportion of positive ESR1 mutation cases after testing.

The main uncertainties regarding the cost-effectiveness of elacestrant are the following:

- Structural uncertainty relating to the use of a post-hoc subgroup analysis to define the target population and outcomes on the basis of duration of prior treatment (progression after at least 12 months of ET+CDK4/6i).
- The lack of comparative data for elacestrant versus the most relevant current treatment options; and reliance on treatment effects from an unanchored MAIC, with small sample sizes and limited availability of prognostic data.
- Selection of overall survival extrapolations for the company's target population (subgroup 1) and the assumed persistence of the relative treatment benefit.
- Assumptions regarding the duration of treatment for comparators, particularly for patients with a dual ESR1 and PIK3CA mutation (subgroup 2).
- The source used for the price of everolimus (BNF versus eMIT). The cost-effectiveness results in this report are based on a confidential discounted price proposed for elacestrant, but only publicly available prices for other drugs. We present results using all drug price discounts available in the NHS in a confidential addendum to this report.

Finally, we note that there is uncertainty over the cost and practical implications for the NHS of introducing a test for ESR1 mutation when treatment with elacestrant is being considered; using either digital PCR methods that would require a repeat tissue biopsy, or with a ctDNA blood test. ctDNA testing is currently available from the North Thames NHS GLH using the Marsden360 assay. We understand that other NHS GLHs are exploring this or a similar approach., and that the cost could fall if NGS panel testing were to be introduced for ESR1 and additional treatment targets as they become available.

7 SEVERITY MODIFIER

7.1 Severity modifier for the company's base case

The company presented their rationale for applying a severity modifier for QALYs in CS section B.3.6. This was calculated using the QALY shortfall calculator estimator (Schneider et al., 2021).[50] This calculator follows NICE recommended methods in the NICE Health Technology Evaluations manual, section 6.2.[24] The following information is required:

- **Mean age of the patient population:** the calculator only accepts integer numbers for age. Therefore, the company considered [redacted] years old for subgroup 1 and [redacted] for subgroup 2 (see CS Table 39).
- **Discount rate:** 3.5% (cost and QALYs) (see CS B.3.2.2.3)
- **The proportion of females in the patient population:** [redacted] (CS Table 39)
- **Remaining QALYs with the disease (discounted):** the company considered the total discounted QALYs from the comparators' results of [redacted] for subgroup 1 and [redacted] for subgroup 2 (see CS Table 81).
- **Scenario:** "Reference case - MVH value set + HSE 2014 ALDVMM model (Hernandez Alava et al.)"

The EAG verified the severity modifier results reported for the company's base case (CS Table 78). Subgroup 1 met the criteria for a QALY severity weight of 1.2 on the basis of proportional shortfall (85% to 95%), but subgroup 2 did not (see Table 45). Neither subgroup met the requirement for a QALY weight based on absolute QALY shortfall (≥12).

Table 45 Severity modifier estimates for the company's base case

	Subgroup 1	Subgroup 2
Mean age of the patient population	[redacted]	[redacted]
Remaining QALYs without the disease	[redacted]	[redacted]
Remaining QALYs with the disease	[redacted]	[redacted]
Absolute shortfall	[redacted]	[redacted]
Proportional shortfall	[redacted]	[redacted]
QALY weight	**1.2**	**1.0**

Source: Produced by the EAG using the Schneider QALY shortfall calculator and information in the CS and model

We assessed the sensitivity of the severity modifier to the baseline age of the modelled population. Varying the mean age did not affect the severity modifier estimate.

7.2 Severity modifier for the EAG's preferred analysis

Using the EAG's preferred analysis, assumptions (see section 6.2) considered the mean age of the population from the Flatiron instead of the EMERALD estimate. Table 46 below shows that the QALYs' weight remained the same for both subgroups.

Table 46 Severity modifier estimates for the EAG's assumptions

	Subgroup 1	Subgroup 2
Mean age of the patient population	[redacted]	[redacted]
Remaining QALYs without the disease	[redacted]	[redacted]
Remaining QALYs with the disease	[redacted]	[redacted]
Absolute shortfall	[redacted]	[redacted]
Proportional shortfall	[redacted]	[redacted]
QALY weight	**1.2**	**1.0**

Source: Produced by the EAG using the Schneider QALY shortfall calculator and information in the CS and model

8 REFERENCES

1. Chandarlapaty S, Chen D, He W, et al. Prevalence of ESR1 Mutations in Cell-Free DNA and Outcomes in Metastatic Breast Cancer: A Secondary Analysis of the BOLERO-2 Clinical Trial. JAMA Oncol 2016;2(10):1310-15. doi: 10.1001/jamaoncol.2016.1279

2. Turner N, Rugo HS, Ciruelos EM, et al. Abstract PD15-01: Impact of ESR1 mutations on endocrine therapy (ET) plus alpelisib benefit in patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), PIK3CA-mutated, advanced breast cancer (ABC) who progressed on or after prior cyclin-dependent kinase inhibitor (CDK4/6i) therapy in the BYLieve trial. Cancer Research 2022;82(4_Supplement):PD15-01. doi: 10.1158/1538-7445.SABCS21-PD15-01

3. Clatot F, Perdrix A, Augusto L, et al. Kinetics, prognostic and predictive values of ESR1 circulating mutations in metastatic breast cancer patients progressing on aromatase inhibitor. Oncotarget 2016;7(46):74448-59. doi: 10.18632/oncotarget.12950

4. Kalinsky K, Accordino MK, Chiuzan C, et al. Randomized Phase II Trial of Endocrine Therapy With or Without Ribociclib After Progression on Cyclin-Dependent Kinase 4/6 Inhibition in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer: MAINTAIN Trial. J Clin Oncol 2023;41(24):4004-13. doi: 10.1200/JCO.22.02392

5. Turner NC, Swift C, Kilburn L, et al. ESR1 Mutations and Overall Survival on Fulvestrant versus Exemestane in Advanced Hormone Receptor-Positive Breast Cancer: A Combined Analysis of the Phase III SoFEA and EFECT Trials. Clin Cancer Res 2020;26(19):5172-77. doi: 10.1158/1078-0432.CCR-20-0224

6. Cardoso F, Costa A, Norton L, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Breast 2014;23(5):489-502. doi: 10.1016/j.breast.2014.08.009

7. NICE. Everolimus with exemestane for treating advanced breast cancer after endocrine therapy: TA421: National Institute for Health and Care Excellence, 2016.

8. NICE. Alpelisib with fulvestrant for treating hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced breast cancer: TA816: National Institute for Health and Care Excellence, 2022.

9. Bardia A. PS17-02 Elacestrant vs standard-of-care in ER+/HER2- advanced or metastatic breast cancer (mBC) with ESR1 mutation: key biomarkers and clinical subgroup analyses from the phase 3 EMERALD trial. SABCS 2023

10. Bardia A, Bidard F-C, Neven P, et al. Abstract GS3-01: GS3-01 EMERALD phase 3 trial of elacestrant versus standard of care endocrine therapy in patients with ER+/HER2- metastatic breast cancer: Updated results by duration of prior CDK4/6i in metastatic setting. Cancer Research 2023;83(5_Supplement):GS3-01. doi: 10.1158/1538-7445.SABCS22-GS3-01

11. Bidard F-C, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. J Clin Oncol 2022;40(28):3246-56. doi: 10.1200/JCO.22.00338

12. Rugo HS, Neven P, Saffie I, et al. Abstract PD13-05: Alpelisib + fulvestrant in patients with PIK3CA-mutated, HR+, HER2— advanced breast cancer (ABC) who received chemotherapy or endocrine therapy (ET) as immediate prior treatment: BYLieve Cohort C primary results and exploratory biomarker analyses. Cancer Research 2022;82(4_Supplement):PD13-05. doi: 10.1158/1538-7445.SABCS21-PD13-05

13. Raphael A, Salmon-Divon M, Epstein J, et al. Alpelisib Efficacy in Hormone Receptor-Positive HER2-Negative PIK3CA-Mutant Advanced Breast Cancer Post-Everolimus Treatment. Genes (Basel) 2022;13(10) doi: 10.3390/genes13101763

14. Stemline Menarini. UK Clinical Expert Opinion, Data on File, 2024.

15. NICE. Fulvestrant for the treatment of locally advanced or metastatic breast cancer TA239: National Institute for Health and Care Excellence, 2011.

16. Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care: York Publishing Services Ltd.: CRD 2009.

17. Stemline Menarini. Clinical Study Report v.2: Elacestrant monotherapy vs. standard of care for the treatment of patients with ER+/HER2- advanced breast cancer following CDK4/6 inhibitor therapy: A phase 3 randomized, open-label, active-controlled, multicenter trial (EMERALD), 2023:4424.

18. NICE. Final scope: Elacestrant for treating oestrogen receptor-positive, HER2-negative advanced breast cancer with an ESR1 mutation after at least 1 endocrine treatment [ID6225]: National Institute for Health and Care Excellence, 2024.

19. Stemline Menarini. Clinical Study Protocol (RAD1901-308) | Elacestrant monotherapy vs. standard of care for the treatment of patients with ER+/HER2- advanced breast cancer following CDK4/6 inhibitor therapy: a Phase 3 randomized, open-label, active-controlled, multicentre trial (EMERALD), 2020:118.

20. Stemline Menarini. Overall Survival Addendum to Clinical Study Report v.2 RAD1901-308 | Elacestrant monotherapy vs. standard of care for the treatment of patients with ER+/HER2- advanced breast cancer following CDK4/6 inhibitor therapy: a Phase 3 randomized, open-label, active-controlled, multicenter trial (EMERALD) | overall survival addendum as of 2nd September 2022, 2023:14.

21. Cuyún Carter G, Mohanty M, Stenger K, et al. Prognostic Factors in Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative (HR+/HER2-) Advanced Breast Cancer: A Systematic Literature Review. Cancer Manag Res 2021;13:6537-66. doi: 10.2147/cmar.S300869 [published Online First: 20210820]

22. Vidal G, Cinfio F, Badaracco J, et al. CO134 Estimating the Direct and Indirect Resource Burden of Treatment Management with Current Standard of Care or Elacestrant for ER+, HER2-, ESR1-Mutated Advanced or Metastatic Breast Cancer Patients: A Population-Level Provider Model. Value in Health 2023;26(12):S38.

23. Zeng W, Cao X, Lin J, et al. Cost-effectiveness analysis of elacestrant versus standard endocrine therapy for second-/ third-line treatment of patients with HR+/HER2- advanced or

metastatic breast cancer: a US payer perspective. Front Oncol 2023:11. doi: 10.3389/fonc.2023.1272586

24. NICE. Introduction to health technology evaluation | NICE health technology evaluations: the manual | Guidance | NICE. 2022

25. Hernandez M, Pudney S. eq5dmap: A command for mapping between EQ-5D-3L and EQ-5D-5L. The Stata journal 2017;18 doi: 10.1177/1536867X1801800207

26. Woods B, Sideris E, Palmer S, et al. NICE DSU technical support document 19: partitioned survival analysis for decision modelling in health care: a critical review: University of Sheffield, 2017.

27. Guyot P, Ades A, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC medical research methodology 2012;12:1-13.

28. Hagiwara Y, Shiroiwa T, Shimozuma K, et al. Impact of Adverse Events on Health Utility and Health-Related Quality of Life in Patients Receiving First-Line Chemotherapy for Metastatic Breast Cancer: Results from the SELECT BC Study. Pharmacoeconomics 2018;36(2):215-23. doi: 10.1007/s40273-017-0580-7

29. Mistry R, May JR, Suri G, et al. Cost-Effectiveness of Ribociclib plus Letrozole Versus Palbociclib plus Letrozole and Letrozole Monotherapy in the First-Line Treatment of Postmenopausal Women with HR+/HER2- Advanced or Metastatic Breast Cancer: A U.S. Payer Perspective. J Manag Care Spec Pharm 2018;24(6):514-23. doi: 10.18553/jmcp.2018.24.6.514

30. Lloyd A, Nafees B, Narewska J, et al. Health state utilities for metastatic breast cancer. Br J Cancer 2006;95(6):683-90. doi: 10.1038/sj.bjc.6603326

31. Telford C, Bertranou E, Large S, et al. Cost-Effectiveness Analysis of Fulvestrant 500 mg in Endocrine Therapy-Naïve Postmenopausal Women with Hormone Receptor-Positive Advanced Breast Cancer in the UK. Pharmacoecon Open 2019;3(4):559-70. doi: 10.1007/s41669-019-0134-3

32. Swinburn P, Lloyd A, Nathan P, et al. Elicitation of health state utilities in metastatic renal cell carcinoma. Current Medical Research and Opinion 2010;26(5):1091–96. doi: https://doi.org/10.1185/03007991003712258

33. Smith-Palmer J, Bae JP, Boye KS, et al. Evaluating health-related quality of life in type 1 diabetes: a systematic literature review of utilities for adults with type 1 diabetes. Clinicoecon Outcomes Res 2016;8:559-71. doi: 10.2147/CEOR.S114699

34. NICE. Ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer: TA496: National Institute for Health and Care Excellence, 2017.

35. NICE. Fulvestrant for untreated locally advanced or metastatic oestrogen-receptor positive breast cancer: TA503: National Institute for Health and Care Excellence, 2018.

36. NICE. Abemaciclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer: TA563: National Institute for Health and Care Excellence, 2019.

37. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health 2010;13(5):509-18. doi: 10.1111/j.1524-4733.2010.00700.x

38. NICE. BNF: British National Formulary - NICE. 2021

39. eMIT. Drugs and pharmaceutical electronic market information tool (eMIT). GOVUK 2023

40. Jerusalem G, Mariani G, Ciruelos EM, et al. Safety of everolimus plus exemestane in patients with hormone-receptor-positive, HER2-negative locally advanced or metastatic breast cancer progressing on prior non-steroidal aromatase inhibitors: primary results of a phase IIIb, open-label, single-arm, expanded-access multicenter trial (BALLET). Ann Oncol 2016;27(9):1719-25. doi: 10.1093/annonc/mdw249

41. Alaklabi S, Roy AM, Attwood K, et al. Real world outcomes with alpelisib in metastatic hormone receptor-positive breast cancer patients: A single institution experience. Front Oncol 2022;12:1012391. doi: 10.3389/fonc.2022.1012391

42. PSSRU. Unit Costs of Health and Social Care. 2022

43. NHS. National Cost Collection for the NHS. 2022

44. NICE. Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer: TA619, 2020.

45. NICE. Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens: TA423: National Institute for Health and Care Excellence, 2016.

46. Jhaveri KL, Jeselsohn R, Ma CX, et al. Imlunestrant, with or without everolimus or alpelisib, in ER+, HER2- advanced breast cancer (aBC): Results from the phase 1a/b EMBER study.

47. Lin NU, Borges VF, Patel MR, et al. Results from the phase 1/2 study of OP-1250, an oral complete estrogen receptor (ER) antagonist (CERAN) and selective ER degrader (SERD) in patients (pts) with advanced or metastatic ER-positive, HER2-negative breast cancer. Annals of Oncology;34(S2):S338. doi: https://doi.org/10.1016/j.annonc.2023.09.559

48. Round J, Jones L, Morris S. Estimating the cost of caring for people with cancer at the end of life: A modelling study. Palliat Med 2015;29(10):899-907. doi: 10.1177/0269216315595203

49. Georghiou T, Davies S, Davies A, Bardsley M. Understanding patterns of health and social care at the end of life: Nuffield Trust, 2012.

50. Schneider P, McNamara S, Love-Koh J, et al. QALY Shortfall Calculator.

9 APPENDICES

Appendix 1 EAG assessment of company's clinical effectiveness systematic literature review methods

Table 47 EAG appraisal of systematic review methods

Systematic review components and processes	EAG response	EAG comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	CS Appendix D Table 4 provides details of the eligibility criteria for the initial clinical SLR (referred to in the submission as "the global clinical SLR"). Criteria were appropriate but broader for interventions and comparators than that of the NICE final scope. CS Appendix D Table 5 provides details of narrower eligibility criteria that aligned with the NICE final scope. These eligibility criteria were appropriate in terms of the appraisal and were used to rescreen included studies identified from the initial SLR
Were appropriate sources of literature searched?	Yes	Searches covered sufficient databases (MEDLINE (Ovid), Embase (Ovid), Cochrane (CENTRAL and CDSR; Ovid)) Relevant grey literature was also searched (conference proceedings from global, US, European and Australasian breast cancer meetings; Government/international bodies; reference lists of included studies)
What time period did the searches span and was this appropriate?	Yes	Database searches were carried out from inception to August 2023. Searches of conference proceedings were limited to meetings held in 2020 to 2023 inclusive. The searches were

Systematic review components and processes	EAG response	EAG comments
		approximately 8 months old when the CS was received by the EAG. The EAG therefore reran the searches with a date limit for the past 8 months.
Were appropriate search terms used and combined correctly?	Yes	Search strategies for MEDLINE, Embase and Cochrane are reported in CS Appendix D.1.1. The searches used an appropriate set of terms to specify the type of breast cancer relevant to the appraisal combined with a broad range of interventions/ comparators including, but not limited to, those for the appraisal. The RCT filter used in the company searches however excludes conference abstracts. The EAG therefore reran the Embase search for the past three years using terms that would include conference abstracts.
Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	Yes	CS Appendix D Table 4 provides details of the initial SLR eligibility criteria, which were appropriate but broader for interventions and comparators than that of the NICE final scope. Appendix D Table 5 provides details of the narrower eligibility criteria, which aligned with the NICE final scope. These eligibility criteria were applied to the included studies identified from the broader SLR and were appropriate.
Were study selection criteria applied by two or more reviewers independently?	Yes	For the initial broader SLR, titles and abstracts and full papers were screened by two independent reviewers. Discrepancies between the reviewers

Systematic review components and processes	EAG response	EAG comments
		was reconciled through consensus (titles and abstracts) or a third independent reviewer (titles and abstracts, full papers) The included publications from the initial SLR were rescreened by two independent reviewers using the narrower eligibility criteria aligned with the NICE scope. Any discrepancies were resolved by a third independent reviewer.
Was data extraction performed by two or more reviewers independently?	Yes	Data were extracted by one reviewer and checked by a second reviewer. The EAG considers this acceptable.
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Yes	The company used the seven-criteria checklist recommended by NICE, based on guidance provided by CRD (CS Appendix D.2.4).
Was risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	Unclear	The CS does not state how the risk of bias assessments were conducted.
Is sufficient detail on the individual studies presented?	Yes	CS section B.2.1 to 2.7, CS Appendix D.2.3 and D.2.4, and CS Appendix E provide methodological details and results from the single relevant trial (EMERALD) identified for this appraisal. The trial CSR was also provided.
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA)	Yes	Due to the absence of individual patient-level data for the comparators and a lack of common comparator, an unanchored

Systematic review components and processes	EAG response	EAG comments
was undertaken, were appropriate methods used?		MAIC was implemented to facilitate an ITC for two outcomes (OS and PFS). Our critique of the MAIC is provided in section 3.4 of this report

Source: Table created by the EAG
CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; CRD, Centre for Reviews and Dissemination; CS, company submission; CSR, clinical study report; EAG, External Assessment Group; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; OS, overall survival; PFS, Progression-free survival; PICOD, population, intervention, comparator, outcome, design; RCT, randomised controlled trial; SLR, systematic literature review

Appendix 2 Prognostic factors included in the company's MAIC

Table 48 below compares prognostic factors identified by Cuyún Carter et al (2021) with those proposed by key opinion leaders consulted by the company. For further discussion please see section 3.4.2 of this EAG report.

Table 48 Comparison of prognostic factors identified by a systematic review by Cuyún Carter et al (2021) with factors proposed by key opinion leaders, and their inclusion status in the MAIC

Prognostic factors with strongest evidence of association with[a]:		Prognostic factors/effect modifiers identified by key opinion leaders (KOLs)[b]	Included in MAIC?
worse OS	worse PFS		
Negative progesterone receptor status		ER expression	*Partial* - Included implicitly through population restriction (focus on ESR1-mut)
Higher tumour grade		Not identified by KOLs	No - Not identified by KOLs
Higher circulating tumour cell (CTC) count and higher Ki67 level	Higher circulating tumour cell (CTC) count,	Not identified by KOLs	No - Not identified by KOLs
Number of metastatic sites (e.g. multiple vs single)	Number and sites of metastases	Number of metastatic sites	No - excluded due to lack of data
Sites of metastases (e.g. presence of liver metastases vs absence),		Bone metastases / bone metastases only; Visceral metastases	No - excluded due to lack of data

Prognostic factors with strongest evidence of association with[a]:		Prognostic factors/effect modifiers identified by key opinion leaders (KOLs)[b]	Included in MAIC?
worse OS	**worse PFS**		
Shorter time to recurrence or progression to advanced breast cancer		Time since original diagnosis	No - discrepancy in data available (only time since stage III diagnosis in Flatiron study)
Poor performance status		ECOG performance status	***Partial*** – approx. 25% of patients had missing performance status.
Prior therapy attributes in the early or metastatic setting (type of therapy, treatment line, response of prior therapy)	Absence of prior therapy or higher lines of therapy in the early or metastatic setting	Length of time on prior CDK4/6i;	***Partial*** - Included implicitly through population restriction (prior CDK4/6i ≥12 months)
		Number of treatment lines in metastatic setting;	**Yes** – for ET lines. Number of prior ET included as only number of prior lines of ET available
		Prior chemotherapy	Yes
Race (black vs white).		Not identified by KOLs	No - Not identified by KOLs
		Histology (ductal vs. lobular)	No - Excluded due to lack of data
		De novo vs. recurrent disease (i.e. diagnosed in adjuvant setting)	No - Excluded due to lack of data
		De novo vs. progressed disease	No - Excluded due to lack of data
		Age	**Yes** - Flatiron patients restricted to 50 years or older

Prognostic factors with strongest evidence of association with[a]:		Prognostic factors/effect modifiers identified by key opinion leaders (KOLs)[b]	Included in MAIC?
worse OS	**worse PFS**		
		Menopausal status	***Partial***. Included implicitly through a focus on postmenopausal women in EMERALD and older women in Flatiron.

Source: reproduced, in part, from CS Table 25
[a] as identified by a systematic review of prognostic factors by Cuyún Carter et al (2021).
[b] As identified through consultation by the company with key opinion leaders (see CS Section B.2.9.1 and CS Table 25)
Dark shaded cells indicate that the prognostic factor was not included in the sub-set of factors judged by Cuyún Carter et al (2021) as having the strongest evidence of association with health outcomes.

Appendix 3 Survival extrapolations: Target population (subgroup 1)

Figure 11 Everolimus + exemestane OS for subgroup 1

Source: Produced from the company's model by the EAG

Figure 12 Elacestrant OS for subgroup 1

Source: Produced from the company's model by the EAG

Figure 13 Everolimus + exemestane PFS for subgroup 1

Source: Produced from the company's model by the EAG

Figure 14 Elacestrant PFS for subgroup 1

Source: Produced from the company's model by the EAG

Figure 15 Elacestrant TTD for subgroup 1

Source: Produced from the company's model by the EAG

Figure 16 Everolimus + exemestant outcomes, subgroup 1 (company base case)

Source: Produced by the EAG from the company model

Figure 17 Elacestrant outcomes, subgroup 1 (company base case)

Source: Produced by the EAG from the company model

Appendix 4 Survival extrapolations: Dual mutated (subgroup 2)

Figure 18 Alpelisib + fulvestrant OS for subgroup 2

Source: Produced from the company's model by the EAG

Figure 19 Elacestrant OS for subgroup 2

Source: Produced from the company's model by the EAG

Figure 20 Alpelisib + fulvestrant PFS for subgroup 2

Source: Produced from the company's model by the EAG

Figure 21 Elacestrant PFS for subgroup 2

Source: Produced from the company's model by the EAG

Figure 22 Elacestrant TTD for subgroup 2

Source: Produced from the company's model by the EAG

Figure 23 Alpelisib + fulvestrant outcomes, subgroup 2 (company base case)

Source: Produced by the EAG from the company model

Figure 24 Elacestrant outcomes, subgroup 2 (company base case)

Source: Produced by the EAG from the company model

Appendix 5 Additional company's scenario analysis

The company's economic model has a scenario module with additional scenarios described below:

Severity modifier: do not consider a severity modifier for subgroup 1 (base case 1.2)

- Elacestrant OS:
  - Subgroup 1: additional scenarios with the exponential (worst BIC fit), generalised Gamma, Gompertz and Weibull (best BIC fit) distributions
  - Subgroup 2: additional scenarios with the exponential (worst statistical fit), generalised Gamma, Gompertz (best statistical fit) and log-logistic distributions
- Comparator OS:
  - Subgroup 1: additional scenarios with the generalised gamma (worst statistical fit), Gompertz, Log-logistic and Log-normal distributions
  - Subgroup 2: additional scenarios with the generalised Gamma, Gompertz, Log-logistic and exponential (worst statistical fit) distributions
- Elacestrant PFS:
  - Subgroup 1: additional scenarios with the exponential, generalised gamma (best statistical fit), Gompertz, Weibull (worst statistical fit), and Gamma distributions
  - Subgroup 2: additional scenarios with the generalised gamma (best statistical fit), Gompertz (worst statistical fit), Weibull, and gamma distributions
- Comparator PFS:
  - Subgroup 1: additional scenarios with the exponential (worst statistical fit), generalised Gamma, Gompertz, and Weibull distributions
  - Subgroup 2: additional scenarios with the exponential (worst statistical fit), log-logistic, Gompertz, and Weibull distributions
- **Elacestrant TTD:** additional scenarios with the exponential, generalised gamma (best statistical fit), Gompertz, Weibull and Gamma (worst statistical fit) distributions
- **ESR1-mut testing cost:** consider the user-defined cost (base case: digital PCR cost)
- **ESR1-mut testing cost approach:** consider non-prevalence-based (base case: prevalence-based)
- **PF health state utility source:** use PF utilities from previous assessments as TA563, TA496, TA503 (base case: EMERALD)
- **PD health state utility source:** use PD utilities from previous assessments as TA563, TA496, TA503 (base case: EMERALD)
- **Health state utility source:** consider a user-defined utility (base case: EMERALD)

- **Capecitabine dose:** consider the minimum (1,000 mg/m^2) and maximum doses (1,250 mg/m^2) (base case: average dose, 1,125 mg/m^2)

For subgroup 1, the ICER varied from £22,804 (elacestrant OS extrapolation using exponential) to £151,291 (elacestrant OS extrapolation using Gompertz distribution). The non-cost-effective scenarios are related to the OS extrapolations for elacestrant and the comparator everolimus + exemestane. Two scenarios are not cost-effective, and the relative QALYs shortfall indicated that the severity modifier 1.2 did not apply to them: the log-logistic distribution was the second-best fit, and the log-normal distribution was the second-worst fit to the OS extrapolation for the comparator (everolimus + exemestane).

For subgroup 2, elacestrant is dominant for all additional scenarios. One scenario could not be performed owing to a lack of model convergence to fit the generalised gamma as an OS extrapolation for elacestrant. Three scenarios modified the total discounted QALYs to a value where the severity modifier 1.2 could be applied: progression disease health state utilities from TA563 and TA496 and generalised gamma as OS extrapolation for alpelisib + fulvestrant.