Single Technology Appraisal

Ribociclib with an aromatase inhibitor for adjuvant treatment of hormone receptor-positive, HER2-negative early breast cancer [ID6153]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ribociclib with an aromatase inhibitor for adjuvant treatment of hormone receptor-positive, HER2-negative early breast cancer [ID6153]

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 Novartis:**
   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
   b. British Oncology Pharmacy Association

4. **Expert personal perspectives** from:
   a. Professor David Cameron – clinical expert, nominated by Novartis
   b. Mr Michal Sladkowski – clinical expert, nominated by British Oncology Pharmacy Association
   c. Eleanor Pearce Willis – patient expert, nominated by Breast Cancer Now
   d. Kirstin Spencer – patient expert, nominated by Independent Cancer Patients' Voice

5. **External Assessment Report** prepared by Liverpool Reviews and Implementation Group

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

Ribociclib with an aromatase inhibitor for the adjuvant treatment of hormone receptor-positive, HER2-negative early breast cancer [ID6153]

Document B

Company evidence submission

30th October 2024

File name	Version	Contains confidential information	Date
ID6153_Ribociclib_NICE_Document B [REDACTED]	Final	No	30th October 2024

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE health technology evaluation guidance development manual.

In this template any information that should be provided in an appendix is listed in a box.

Highlighting in the template (excluding the contents list)

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Grey highlighted text in the footer does not work as an automatic form field, but serves the same purpose – as prompt text to show where you need to fill in relevant details. Replace the text highlighted in [grey] in the header and footer with appropriate text. (To change the header and footer, double click over the header or footer text. Double click back in the main body text when you have finished.)

Contents

Tables and figures

Abbreviations

Abbreviation	Definition
ABC	Advanced breast cancer
AESI	Adverse event of special interest
AI	Aromatase inhibitor
AJCC	American Joint Committee on Cancer
AKT	Protein kinase B (Akt)
ALN	Axillary lymph node
ATAC	Arimidex, Tamoxifen, Alone or in Combination trial
ATC	Anatomical therapeutic chemical classification
BC	Breast cancer
BIC	Bayesian information criterion
BL	Baseline
BMI	Body mass index

BNF	British National Formulary
BRCA	Breast cancer gene
CADTH	Canadian Agency for Drugs and Technologies in Health
CDK	Cyclin-dependent kinase
CEA	Cost-effectiveness analysis
CHMP	Committee for Medicinal Products for Human Use
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
CYP	Cytochrome P450
DDFS	Distant disease-free survival
DR	Disease recurrence
DSA	Deterministic sensitivity analysis
DSU	Decision support unit
EAG	Evidence assessment group
EBC	Early breast cancer
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EEPRU	Economic Evaluation of Health and Social Care Interventions Policy Research Unit
EHR	Electronic health record
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End of treatment
EQ-5D	EuroQol-5 Dimensions
ER	Oestrogen receptor
ESMO	European Society for Medical Oncology
ESS	Effective sample size
ET	Endocrine therapy
FAS	Full analysis set
FUL	Fulvestrant
GEE	Generalised estimating equations
GLM	Generalised linear model
HADS	Hospital anxiety and depression scale
HR	Hazard ratio
HRT	Hormone replacement therapy
HTA	Health Technology Assessment
IA	Interim analysis
ICER	Incremental cost-effectiveness ratio
IDF	Invasive disease free
IDFS	Invasive disease-free survival
IM	Intramuscular
IPD	Individual patient data

IRT	Interactive response technology system
ISH	In-situ hybridisation
ITC	Indirect treatment comparison
ITT	Intent-to-treat
LHRH	Luteinising hormone-releasing hormone
LRRFS	Locoregional recurrence-free survival
MAIC	Matching-adjusted indirect comparison
MHRA	Medicines and Healthcare products Regulatory Agency
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Not estimable
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NMA	Network meta-analysis
NMR	Non-metastatic recurrence
NR	Not reported
NSAI	Non-steroidal aromatase inhibitor
OFS	Ovarian function suppression
OS	Overall survival
PA	Pathological assessment
PAS	Patient access scheme
PBAC	Pharmaceutical Benefits Advisory Committee
PC	Pharmacokinetics
PDR	Proportion distant recurrence
PFS	Progression-free survival
PH	Proportional hazards
PICO	Population, intervention, comparator, outcome
PIK	Phosphoinositide 3-kinase
PK	Pharmacokinetics
PNMR	Proportion non-metastatic recurrence
PPS	Post-progression survival
PR	Progesterone receptors
PRO	Patient-reported outcome
PSM	Partitioned survival model
PSPM	Proportion secondary primary malignancy
PSS	Personal social services
QALY	Quality-adjusted life year
QIC	Quasi-Akaike information criterion
QLQ	Quality of life questionnaire
R	Restricted
RCS	Restricted cubic splines
RCT	Randomised controlled trial
RDI	Relative dose intensity

RFS	Recurrence-free survival
RIB	Ribociclib
ROW	Rest of world
RW	Real world
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SEM	Standard error of the mean
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SMD	Standardised mean difference
SPM	Second primary malignancy
STA	Single technology appraisal
STEEP	Standardised definitions for efficacy end points
TAG	Technology appraisal guidance
TEAE	Treatment-emergent adverse event
TNM	Tumour, node, metastasis
TOR	Target of rapamycin
TSD	Technical support document
TTD	Time to treatment discontinuation
TX	Treatment
U	Unrestricted
UK	United Kingdom
USA	United States of America
VAS	Visual analogue scale
WHO	World Health Organisation
WPAI	Work productivity and activity impairment
WTP	Willingness to pay

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The anticipated marketing authorisation extension for ribociclib in the indication under consideration in this submission is: ribociclib in combination with an aromatase inhibitor (AI) [redacted]

There is no universally accepted definition of high-risk EBC and therefore the term "at high risk of recurrence" is defined as per the NATALEE trial (the pivotal trial for ribociclib in this indication) inclusion criteria, as adult patients with HR+/HER2– EBC that is:[2]

- Anatomical Stage IIA
  - N0 with either:
    - Grade 3, or
    - Grade 2, with any of the following criteria: Ki67 ≥20%, Oncotype DX, Breast Recurrence Score ≥26, Prosigna/PAM50 categorised as high risk, MammaPrint categorised as high risk or EndoPredict EPclin Risk Score categorised as high risk
  - N1
- Anatomical Stage IIB
  - N0 or N1
- Anatomical Stage III
  - N0, N1, N2 or N3

Ribociclib is already licensed by the European Medicines Agency (EMA) for the treatment of women with HR+/HER2– locally advanced or metastatic breast cancer in combination with an AI or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy (ET).[3] Ribociclib in combination with fulvestrant has been previously evaluated by NICE in 2021 (TA687), and received a positive recommendation for the treatment of women with HR+/HER2– locally advanced or metastatic breast cancer in adults who have had previous ET.[4] Ribociclib in combination with an AI has also been evaluated by NICE in 2017 (TA496), and received a positive recommendation for initial endocrine-based therapy in adults with HR+/HER2– locally advanced or metastatic breast cancer.[5]

The decision problem addressed within this submission is presented in Table 1. The target patient population is aligned with the full anticipated marketing authorisation extension for ribociclib in this indication and the population included in the NATALEE trial.[1, 2] The population specified in the NICE final scope ("Adults with HR+/HER2– EBC after surgery of the primary breast tumour"; see Table 1) is therefore broader than the target patient population addressed within this submission, and the anticipated marketing authorisation extension.[1]

This submission will consider four populations eligible for treatment with ribociclib:

Base case: *Population 1 (NATALEE ITT)*

The base case population is comprised of patients with HR+/HER2– EBC at high risk of recurrence. The comparator in this population is ET. This population is defined as per the NATALEE inclusion criteria, as adult patients with HR+/HER2– EBC that is:[2]

- Anatomical Stage IIA
  - N0 with either:
    - Grade 3, or
    - Grade 2, with any of the following criteria: Ki67 ≥20%, Oncotype DX, Breast Recurrence Score ≥26, Prosigna/PAM50 categorised as high risk, MammaPrint categorised as high risk or EndoPredict EPclin Risk Score categorised as high risk
  - N1
- Anatomical Stage IIB
  - N0 or N1
- Anatomical Stage III
  - N0, N1, N2 or N3

Subgroups

Population 2 (NATALEE node-positive high-risk)

This population consists of patients with node-positive HR+/HER2– EBC at high risk of recurrence that were eligible for the NATALEE trial. The comparator in this population is ET. This population is defined as per the NATALEE trial, as patients with HR+/HER2– EBC that is:[2]

- Anatomical Stage IIA
  - N1
- Anatomical Stage IIB
  - N1
- Anatomical Stage III
  - N1, N2 or N3

Population 3 (NATALEE node-negative high-risk)

This population consists of patients with node-negative HR+/HER2– EBC at high risk of recurrence that were eligible for the NATALEE trial. The comparator in this population is ET. This population is defined as per the NATALEE trial, as patients with HR+/HER2– EBC that is:[2]

- Anatomical Stage IIA
  - N0 with either:
    - Grade 3, or
    - Grade 2, with any of the following criteria: Ki67 ≥20%, Oncotype DX, Breast Recurrence Score ≥26, Prosigna/PAM50 categorised as high risk, MammaPrint categorised as high risk or EndoPredict EPclin Risk Score categorised as high risk

- Anatomical Stage IIB
  - N0
- Anatomical Stage III
  - N0

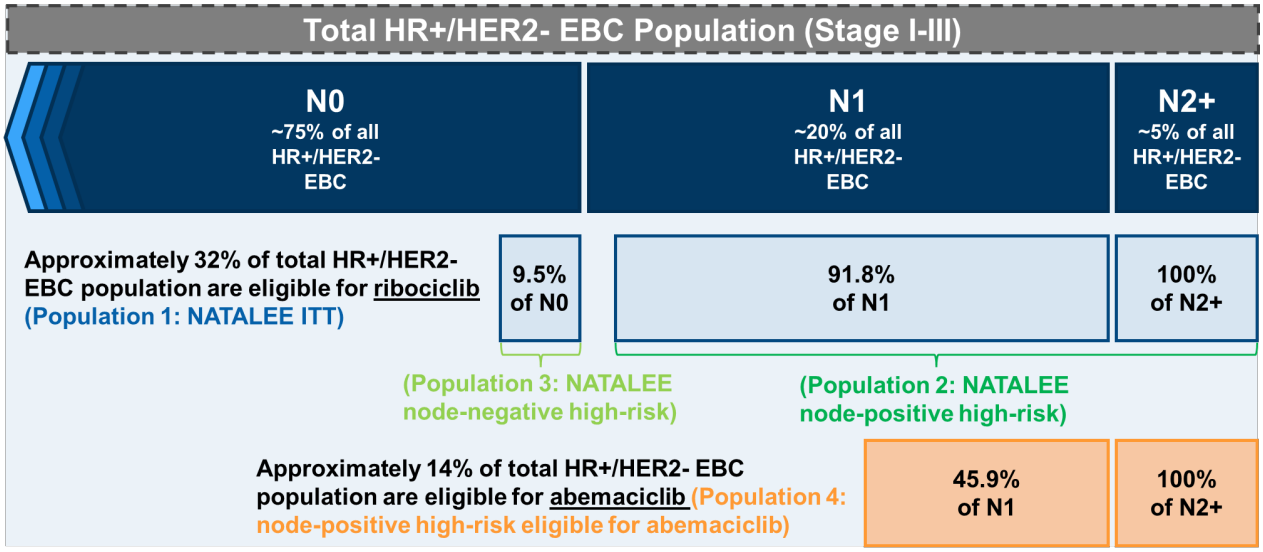
Population 4 (node-positive high-risk eligible for abemaciclib)

This population consists of patients with node-positive HR+/HER2– EBC at high risk of recurrence that are eligible for abemaciclib. The comparators in this population are abemaciclib plus ET and ET. This population is defined as per the technology appraisal guidance (TAG) for abemaciclib in TA810 as node-positive HR+/HER2– EBC with pathological tumour involvement in:[6]

- ≥4 ipsilateral axillary lymph nodes (ALNs), or
- 1–3 ALNS with either:
  - grade 3 disease, or
  - primary tumour size ≥5 cm

Figure 1 depicts the population of patients with HR+/HER2– EBC eligible to receive ribociclib based on its anticipated marketing authorisation extension (Population 1 [NATALEE ITT]).[1] The subgroup Populations 2–4 are also presented.

Figure 1: Patients with HR+/HER2– EBC eligible for treatment with ribociclib and the four populations addressed within this submission



Footnotes: N0: no cancer in lymph nodes; N1: cancer has spread to 1–3 axillary lymph nodes or internal mammary lymph nodes; N2: cancer has spread to at least 4 axillary lymph nodes or it has enlarged the internal mammary lymph nodes spread to or lymph nodes around the collar bone.
Abbreviations: EBC: early breast cancer; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; ; ITT: intention-to-treat; N: node.
Source: Adapted from Tarantino *et al.* (2024).[7]

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	Adults with HR+/HER2– EBC after surgery of the primary breast tumour.	Adults with HR+/HER2– EBC at high risk of recurrence after surgery of the primary breast tumour.	The population specified in the NICE final scope is broader than the target patient population addressed within this submission.
			
			The patient population addressed within this submission (Population 1 [NATALEE ITT]: adults with HR+/HER2– EBC at high risk of recurrence]) is in line with the anticipated marketing authorisation extension for ribociclib in this indication.
			
			The criteria used to define "high risk of recurrence" is aligned to the following criteria used in the NATALEE trial (the pivotal trial for ribociclib in this indication), as adult patients with HR+/HER2– EBC that is:
			• Anatomical Stage IIA
			  ○ N0, with
			  ▪ Grade 3, or
			  ▪ Grade 2, with any of the following criteria: Ki67 ≥20%, Oncotype DX, Breast Recurrence Score ≥26, Prosigna/PAM50 categorised as high risk, MammaPrint categorised as high risk, or EndoPredict EPclin Risk Score categorised as high risk
			  ○ N1
			• Anatomical Stage IIB:
			  ○ N0 or N1
			• Anatomic Stage III:
			  ○ N0, N1, N2 or N3
			
			Treatment after surgery of the primary breast tumour is referred to as adjuvant therapy throughout this submission.

Intervention	Ribociclib with an aromatase inhibitor.	Ribociclib plus AI.	N/A – in line with the NICE final scope.
Comparator(s)	Full population: • Standard ET	**Population 1 (NATALEE ITT):** (HR+/HER2– EBC at high risk of recurrence,	Olaparib has not been included as a comparator to ribociclib plus AI in this submission. As recommended in ESMO Clinical Practice Guidelines for EBC, Novartis understand that patients with EBC who test positive for a BRCA1/2 gene mutation will receive targeted treatment with olaparib before

	For node-positive EBC at high risk of recurrence: • Abemaciclib (with ET) For high-risk EBC with BRCA1 or 2 mutations: • Olaparib (with or without ET)	defined per the NATALEE inclusion): • Standard ET (anastrozole, letrozole, exemestane and tamoxifen) For comparators considered in the subgroup analyses, see 'Subgroups' below.	ribociclib,[8] with this view being validated through discussions with six UK clinical experts at two advisory boards held by the Company in November 2023 and September 2024, who also noted that within the population relevant to this submission, there are very few patients with a BRCA1/2 gene mutation (see Appendix Q). A positive recommendation for ribociclib in HR+/HER2– EBC as an adjuvant therapy would not displace the use of olaparib in patients with BRCA mutation-positive HER2– high-risk EBC after chemotherapy. As such, Novartis do not regard olaparib as a comparator to ribociclib plus AI in this submission.
Outcomes	The outcome measures to be considered include: • overall survival • invasive disease-free survival • distant disease-free survival • adverse effects of treatment • health-related quality of life	The outcome measures considered in this submission include: • overall survival • invasive disease-free survival • distant disease-free survival • adverse effects of treatment • health-related quality of life	N/A – in line with the NICE final scope.
Economic analysis	The cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the	As per the NICE reference case.	N/A – in line with the NICE final scope.

	technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.		
Subgroups to be considered	If the evidence allows the following subgroups will be considered: Node positive/negative disease Risk of recurrence Presence of germline BRCA1 or 2 mutations	This submission considers the following three subgroups (with the relevant comparators listed accordingly): **Population 2 (NATALEE node-positive high-risk)**; defined as per the NATALEE trial for patients with node-positive disease: • ET **Population 3 (NATALEE node-negative high-risk)**; defined as per the NATALEE trial for patients with node-negative disease:	Clinical data and economic analyses are presented for ribociclib plus AI vs ET in Population 2 (NATALEE node-positive high-risk) and Population 3 (NATALEE node-negative high-risk). Abemaciclib is not considered a relevant comparator in Population 2 (NATALEE **node-positive** high-risk) because not all patients within this subgroup are eligible for abemaciclib. The population in which abemaciclib is recommended is a narrower subpopulation of this subgroup.[6] Similarly, abemaciclib is not considered a relevant comparator in Population 3 (NATALEE **node-negative** high-risk) because it is not recommended for patients with node-negative disease.[6] Clinical data and economic analyses are presented for ribociclib plus AI vs abemaciclib plus ET and vs ET in Population 4 (node-positive high-risk eligible for abemaciclib), as defined in the NICE recommendation for abemaciclib in TA810.[6] Finally, as detailed under the 'Comparators' section above, a positive recommendation for ribociclib in HR+/HER2– EBC as an adjuvant therapy

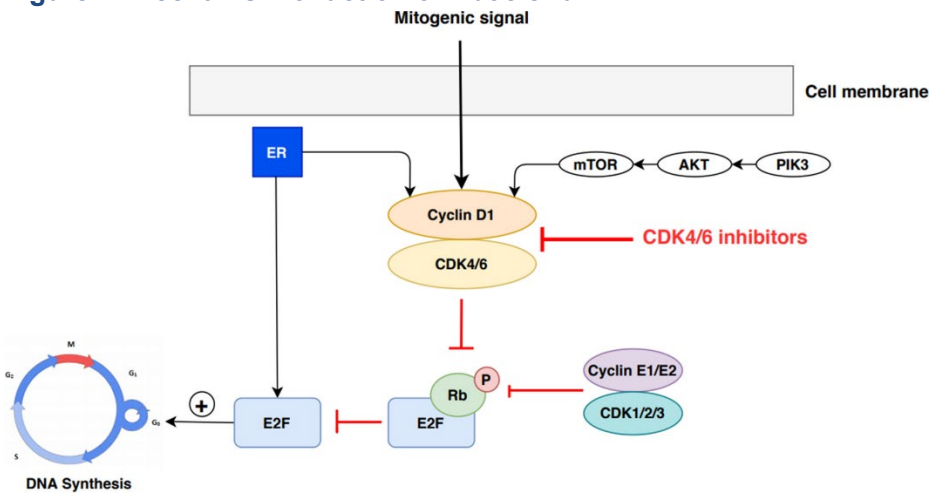
		• ET **Population 4 (node-positive high-risk eligible for abemaciclib)**; defined as per TA810:[6] • Abemaciclib plus ET • ET	would not displace the use of olaparib in patients with BRCA mutation-positive HER2– high-risk EBC after chemotherapy. Therefore, subgroup analyses in patients with germline BRCA1 or 2 mutations have not been conducted for this submission.
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	Novartis do not consider there to be any equality concerns related to this appraisal. The anticipated licence for ribociclib in this indication will include both men and women, as included in the trial. However, as breast cancer occurs more commonly in women than men across the general population, the evidence submitted to support this appraisal will be heavily weighted towards women. As this is consistent with the sexual distribution of the disease within the general population, this is not anticipated to impede appraisal in the overall population of both sexes.	N/A.

Abbreviations: AI: aromatase inhibitor; BRCA: BReast Cancer gene; EBC: early breast cancer; ESMO: European Society for Medical Oncology; ET: endocrine therapy; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; ITT: intention-to-treat; N: node; N/A: not applicable; NHS: national health service; NICE: National Institute for Health and Care Excellence.

B.1.2 Description of the technology being evaluated

A description of the technology being evaluated (ribociclib [Kisqali®]) is presented below in Table 2. The draft Summary of Product Characteristics (SmPC) that includes ribociclib in the indication of relevance to this submission is provided in the reference pack accompanying this submission.[1]

Table 2: Technology being appraised

UK approved name and brand name	UK approved name: Ribociclib Brand name: Kisqali®
Mechanism of action	Ribociclib is a selective inhibitor of cyclin-dependent kinase 4 and 6 (CDK4/6).[9-11] CDK4/6 are members of a family of enzymes involved in the regulation of the G1–S phase of the cell cycle.[9] Imbalance of the cyclin D–CDK pathway is known to be associated with a proliferative phenotype in cancer cells.[10] By preventing interaction between CDK4/6 and cyclin D, ribociclib inhibits the phosphorylation of the retinoblastoma (Rb) tumour suppressor protein thereby blocking the progression from the G1 to the S phase of the cell cycle.[10] The mechanism of action of ribociclib is especially important in HR+ breast cancer, in which responsiveness and resistance to ET is understood to be linked to CDK/cyclin D/Rb activity. CDK4/6 inhibition has been shown to block cell cycle progression in endocrine-resistant breast cancer cells.[12] The mechanism of action of ribociclib is presented in Figure 2. AIs, including NSAIs (e.g. letrozole and anastrozole) and steroidal AIs (exemestane), act by targeting and binding to the aromatase enzyme (irreversibly in the case of exemestane), thus antagonising the conversion of androgens to oestrogens.[13] The use of ribociclib in combination with AIs therefore employs the dual approach of inhibiting cellular proliferation and limiting oestrogen production, achieving better control of micro-metastatic disease. **Figure 2: Mechanism of action of ribociclib**  **Abbreviations**: AKT: protein kinase B; CDK: cyclin-dependent kinase; E2F: elongation factor 2; ER: oestrogen receptor; mTOR: mammalian target of rapamycin; Rb: retinoblastoma; P: phosphorylated; PIK3: phosphoinositide 3-kinase. **Source**: Braal *et al.* (2021).[14]

Marketing authorisation/CE mark status	The anticipated marketing authorisation extension for ribociclib in the indication under consideration in this submission is: [redacted]
	
	"At high risk of recurrence" is defined as per the NATALEE trial (the pivotal trial for ribociclib in this indication) inclusion criteria, as adult patients with HR+/HER2–EBC and:
	• Anatomical Stage IIA
	  ○ N0, with
	  ▪ Grade 3, or
	  ▪ Grade 2, with any of the following criteria: Ki67 ≥20%, Oncotype DX , Breast Recurrence Score ≥26, Prosigna/PAM50 categorised as high risk, MammaPrint categorised as high risk, or EndoPredict EPclin Risk Score categorised as high risk
	  ○ N1
	• Anatomical Stage IIB:
	  ○ N0, N1
	• Anatomic Stage III:
	  ○ N0, N1, N2, or N3
	
	A marketing authorisation extension application for ribociclib in this indication was submitted to the EMA in [redacted]; a positive opinion from the CHMP was received on [redacted].[15] MHRA approval is expected to be received via the International Recognition Procedure aligned to the EMA. Submission to the MHRA is anticipated in [redacted]; the anticipated date of EMA approval is [redacted] while the anticipated date of MHRA approval is [redacted]

Indications and any restriction(s) as described in the SmPC	Ribociclib is already licensed by EMA for the treatment of women with HR+/HER2– locally advanced or metastatic breast cancer in combination with an AI or fulvestrant as initial endocrine-based therapy, or in women who have received prior ET.[3] Ribociclib in combination with fulvestrant has been previously evaluated by NICE in 2021 (TA687), and received a positive recommendation for the treatment of women with HR+/HER2– locally advanced or metastatic breast cancer in adults who have had previous ET.[4] Ribociclib in combination with an AI has also been evaluated by NICE in 2017 (TA496), and received a positive recommendation for initial endocrine-based therapy in adults with HR+/HER2– locally advanced or metastatic breast cancer.[5]
Method of administration and dosage	Ribociclib is available as a tablet and is administered orally.[1] The recommended dose in EBC is 400 mg (two 200 mg film-coated tablets) once daily for 21 consecutive days followed by seven days off treatment, resulting in a complete treatment cycle of 28 days.[1] In patients with HR+/HER2– EBC at high risk of recurrence, ribociclib should be continued until completion of three years of treatment or until disease recurrence or unacceptable toxicity occur.[1] Ribociclib should be used in combination with an AI. In pre- and perimenopausal women, or in men, the AI should be combined with an LHRH agonist. When ribociclib is used in combination with an AI, the AI should be taken orally once daily continuously throughout the 28-day treatment cycle.[1] Please refer to the SmPC of the AI for additional details.
Additional tests or investigations	No additional tests or investigations are required to determine eligibility for ribociclib in this indication, beyond those already routinely conducted in NHS clinical practice for ribociclib in the metastatic/advanced disease setting.

<table>
<tr><td>List price and average cost of a course of treatment</td><td>The list prices for ribociclib are reported below.<table><tr><th>Drug strength</th><th>Pack size</th><th>List price</th></tr><tr><td>Ribociclib 400 mg</td><td>42 tablets (200 mg tablets)</td><td>£1,966.67</td></tr><tr><td>Ribociclib 200 mg</td><td>21 tablets (200 mg tablets)</td><td>£983.33</td></tr></table></td></tr>
<tr><td>Patient access scheme (if applicable)</td><td>A confidential simple PAS of [redacted]% exists for ribociclib which enables the NHS to procure ribociclib at a net price lower than the list price. The confidential PAS prices for ribociclib are reported below.<table><tr><th>Drug strength</th><th>Pack size</th><th>PAS price</th></tr><tr><td>Ribociclib 400 mg</td><td>42 tablets (200 mg tablets)</td><td>[redacted]</td></tr><tr><td>Ribociclib 200 mg</td><td>21 tablets (200 mg tablets)</td><td>[redacted]</td></tr></table></td></tr>
</table>

Abbreviations: AI: aromatase inhibitor; CDK4/6: cyclin-dependent kinase; CHMP: Committee for Medicinal Products for Human Use; EBC: early breast cancer; EMA: European Medicines Agency; ET: endocrine therapy; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; LHRH: luteinizing hormone-releasing hormone; NSAI: non-steroidal aromatase inhibitor; PAS: patient access scheme; Rb: retinoblastoma; SmPC: summary of product characteristics.

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

Early breast cancer

- Approximately 56,800 new cases of breast cancer are diagnosed each year in the UK.[16] It is the fourth most common cause of cancer death in the UK, accounting for approximately 11,500 deaths in women, and 85 deaths in men every year.[16]
- Breast cancer can be categorised into four pathological subtypes, identified by the presence (+) or absence (–) of two types of tumour receptor: HR (a protein receptor to which a hormone [e.g. oestrogen or progesterone] can bind) and HER2 (a transmembrane receptor protein key to cell growth and differentiation). HR+/HER2– breast cancer is the most common subtype, representing 68% of all breast cancers.[17]
- Approximately 80% of breast cancers are diagnosed as Stage I–III disease (which is considered EBC).[18] The target patient population for ribociclib in this submission is in line with the anticipated marketing authorisation extension for ribociclib in this indication and the eligibility criteria of the pivotal NATALEE trial, i.e., patients with HR+/HER2– EBC at high risk of recurrence (Population 1 [NATALEE ITT]; see full population definition in Section B.1.1).

Current clinical management

- Treatment for EBC is of curative intent and aims to prevent disease recurrence. NICE Guideline 101 recommends a combination of surgery and appropriate systemic therapy ([neo]adjuvant therapy) for patients with EBC, unless significant comorbidity precludes surgery.[19]
- Current adjuvant therapy options for patients with HR+/HER2– EBC are limited to ET (e.g. tamoxifen or an AI) with or without bisphosphonates, or abemaciclib plus ET for a subgroup of node-positive HR+/HER2– EBC patients considered to be at high risk of recurrence as per NICE TA810 (see Population 4 [node-positive high-risk eligible for abemaciclib] definition in Section B.1.1).[6, 19]
- For HR+/HER2– EBC patients treated with ET, the risk of breast cancer recurrence persists long term; the 20-year risk of recurrence in HR+/HER2– EBC patients ranges from 10–41% dependent on the anatomical and biological risk factors of the disease,[20] and over 50% of these recurrences occur more than 5 years post diagnosis.[21] Fear of breast cancer recurrence detrimentally impacts patients' psychological wellbeing.[22] Recurrent disease can be local or distant; distant recurrence (i.e., metastases) represents advanced or metastatic breast cancer which is considered incurable, detrimentally impacts patients' wellbeing, and substantially increases patients' risk of death from breast cancer.[20] It is critical to employ effective treatment options early on in breast cancer care to prevent disease progression and disease recurrence long term.
- In 2022, NICE recommended abemaciclib plus ET for the treatment of a subgroup of node-positive HR+/HER2– EBC patients at high risk of recurrence (TA810).[6] This population (referred to as Population 4 [node-positive high-risk eligible for abemaciclib]) is based on several criteria including nodal status, tumour size and disease grade.[6] Notably, patients with node-negative HR+/HER2– EBC at high risk of recurrence (representing 23% of all HR+/HER2– EBC patients at high risk of recurrence) and

patients with N1 disease without additional specific anatomical risk factors (representing 35% of all HR+/HER2– EBC patients at high risk of recurrence) are not eligible for treatment with abemaciclib plus ET.[7] The recurrence rates for these patients are significant; at just 7 years post-treatment, the incidence of overall recurrence is 16.9% and 17.1%, respectively.[23, 24]

Unmet need

- Reducing the risk of disease recurrence in patients with both node-positive HR+/HER2– EBC and node-negative disease with high-risk features, where the risk of recurrence has been shown to be significant, is critically important due to the considerably worsened prognoses of patients who experience a disease relapse.[23]
- Therefore, there is a substantial unmet need for an alternative treatment option that is effective in reducing the risk of recurrence among the broad population of HR+/HER2– EBC patients that are at high risk of their disease returning (Population 1 [NATALEE ITT]), particularly for those who are not eligible for abemaciclib plus ET.
- Ribociclib is an orally administered, potent and highly selective small-molecular inhibitor of CDK4 and CDK6, and has the potential to address this unmet need. Ribociclib has already demonstrated efficacy and favourable long-term safety in advanced or metastatic breast cancer; notably, ribociclib is the only CDK4/6 inhibitor to show a significant and consistent overall survival (OS) advantage in three large Phase III trials in HR+/HER2– advanced or metastatic breast cancer in both pre- and post-menopausal patients.[25-27]
- Results from NATALEE (the pivotal trial for ribociclib in HR+/HER2– EBC at high risk of recurrence) demonstrated that treatment with ribociclib plus AI resulted in [redacted] and clinically meaningful improvements in invasive disease-free survival (iDFS), recurrence-free survival (RFS) and distant disease-free survival (DDFS) vs AI (detailed in Section B.2), thereby providing a promising new treatment option for all HR+/HER2– EBC patients that are at high risk of their disease returning.[28]

B.1.3.1 Disease overview

Pathophysiology and clinical presentation of breast cancer

Breast cancer is a tumour that starts within the breast tissue; it primarily affects women, although it can also occur in men. Breast cancer develops when abnormal cells within the breast multiply and grow uncontrollably, forming a tumour that can invade nearby tissues and potentially spread to other parts of the body.[29]

Both modifiable and non-modifiable factors can influence the likelihood of developing breast cancer. Non-modifiable factors include age, sex, family history and reproductive history, while modifiable factors include weight, alcohol consumption, and exposure to hormonal replacement therapy.[30]

Breast cancer typically first presents as a lump or area of thickened breast tissue, while other common symptoms include nipple discharge (other than breast milk), breast or nipple pain, rashes around or on the nipple, nipple retraction, swollen lymph nodes in the armpit or near the collar bone, and skin dimpling on the breast.[31] Individuals presenting with symptoms of breast cancer in the UK are referred to specialist breast clinics to undergo clinical examinations and

diagnostic investigations such as mammograms, breast ultrasounds and biopsies.[32] Additionally, in UK clinical practice, all women aged between 50 and 70 are invited for breast screening every 3 years.[33] An understanding of the specific symptoms of breast cancer, in combination with the established regular screening program, enables a high proportion of breast cancers in the UK to be diagnosed at a much earlier, and more treatment-amenable, stage.

B.1.3.2 Key prognostic factors in breast cancer

Prognostic factors in breast cancer are factors or characteristics which help to distinguish the likelihood of disease progression, recurrence, and patient survival. Key prognostic factors in breast cancer cover several aspects of the tumour biology, including the pathological subtype, stage, grade and biological risk factors. It is the combination and interplay between these factors that determine patients' breast cancer prognosis and risk of recurrence (see Section B.1.3.5).

Pathological subtype

Breast cancer can be categorised into four pathological subtypes, identified by the presence or absence of two types of tumour receptor. Expression of different receptors on cancerous cells affects patient prognosis.[34] The first is HRs such as oestrogen receptors (ER) and/or progesterone receptors (PR). HRs are activated upon binding of oestrogen or progesterone, which signals cancerous cells to grow. Growth of these cancers is therefore hormone dependent.

Breast cancer cells are also categorised by HER2 (a transmembrane receptor protein key to cell growth and differentiation) expression. Breast cancer cells are assigned HER2 status based on immunohistochemistry (IHC) testing and additional in situ hybridisation (ISH) testing if required.[35] Approximately 80% of all breast cancers typically have HER2– status.[36, 37] The most common subtype of breast cancer is HR+/HER2–, accounting for 68% of all breast cancers, and this is the subtype of relevance to this submission.[17]

Stage

The stage of a cancer describes the extent of its development in the body and is a further key prognostic factor in breast cancer. Breast cancer is most commonly staged using the American Joint Committee on Cancer (AJCC) Tumour, Nodes, Metastases (TNM) system.[38] Based on the pathological stage of the cancer, individual T, N and M stages are used:

- T describes the extent of the primary tumour, including how far it has grown and if it has reached nearby structures or organs
- N describes the extent of cancer spread to nearby lymph nodes; breast cancers are considered node-positive if at least one ALN contains cancerous cells
- M describes the presence of metastasis to other parts of the body

The TNM staging in breast cancer is summarised in Table 3 below. The numbers following each category provide further detail about the extent and spread of the tumour, with a higher number indicating more advanced progression, and ultimately poorer prognosis (see Section B.1.3.5). EBC refers to patients with Stage I–III disease where malignant cells are not detected beyond the breast and nearby lymph nodes.[39]

Table 3: TNM staging system in breast cancer

Stage	TNM	Cytology
0	Tis, N0, M0	This is a pre-cancer of the breast. Many consider DCIS as the earliest form of breast cancer. In DCIS, cancer cells are still present within a duct and have not invaded deeper into the surrounding fatty breast tissue. Paget's disease of the nipple (without an underlying tumour mass) is also Stage 0. In all cases, the cancer has not spread to the lymph nodes or distant sites
IA	T1, N0, M0	The tumour size is 2 cm (approximately 3/4 of an inch) or less across (T1) and has not spread to the lymph nodes (N0) or distant sites (M0)
IB	T0, N1mi, M0 T1, N1mi, M0	The tumour size is 2 cm or less across (or is not found; T0 or T1) with micro-metastases in 1–3 axillary lymph nodes (the tumour size in the underarm lymph nodes is greater than 0.2 mm across and/or more than 200 cells but is not larger than 2 mm; N1mi). The cancer has not spread to distant sites (M0)
IIA	T0, N1, M0 T1, N1, M0	The tumour size is 2 cm or less across (or is not found; T1 or T0) and either: • It has spread to 1–3 axillary (underarm) lymph nodes, with the cancer in the lymph nodes being larger than 2 mm across (N1a) OR • Tiny amounts of tumours are found in the internal mammary lymph nodes (nodes near the breastbone) on a sentinel lymph node biopsy (N1b), OR • It has spread to 1–3 axillary lymph nodes and to the internal mammary lymph nodes (found on a sentinel lymph node biopsy; N1c) • The cancer has not spread to distant sites (M0)
	T2, N0, M0	The tumour size is larger than 2 cm but less than 5 cm (approximately 2 inches) across (T2) but has not spread to the lymph nodes (N0). The cancer has not spread to distant sites (M0)
IIB	T2, N1, M0	The tumour size is larger than 2 cm but less than 5 cm across (T2). It has spread to 1–3 axillary lymph nodes and/or tiny amounts of cancer are found in the internal mammary lymph nodes on a sentinel lymph node biopsy (N1). The cancer has not spread to distant sites (M0)
	T3, N0, M0	The tumour size is larger than 5 cm across but does not grow into the chest wall or skin (T3). The cancer has not spread to the lymph nodes (N0) or to distant sites (M0)
IIIA	T0, N2, M0 T1*, N2, M0 T2, N2, M0	The tumour is not more than 5 cm across (or cannot be found; T0–T2). It has spread to 4–9 axillary lymph nodes or it has enlarged the internal mammary lymph nodes (N2). The cancer has not spread to distant sites (M0)
	T3, N1, M0 T3, N2, M0	The tumour size is larger than 5 cm across but does not grow into the chest wall or skin (T3). It has spread to 1–9 axillary nodes or to internal mammary nodes (N1 or N2). The cancer has not spread to distant sites (M0)
IIIB	T4, N0, M0 T4, N1, M0 T4, N2, M0	The tumour has grown into the chest wall or skin (T4), and one of the following applies: • It has not spread to the lymph nodes (N0) • It has spread to 1–3 axillary lymph nodes and/or tiny amounts of cancer are found in the internal mammary lymph nodes on a sentinel lymph node biopsy (N1) • It has spread to 4–9 axillary lymph nodes, or it has enlarged the internal mammary lymph nodes (N2) The cancer has not spread to distant sites (M0). Inflammatory breast cancer is classified as T4d and is at least Stage IIIB. If it has spread to

		many nearby lymph nodes (N3), then it could be Stage IIIC and, if it has spread to distant lymph nodes or organs (M1), then it would be Stage IV
IIIC	Any T, N3, M0	The tumour is of any size (or cannot be found), and one of the following applies: • The cancer has spread to 10 or more axillary lymph nodes (N3) • The cancer has spread to the lymph nodes under the collar bone (infraclavicular nodes; N3) • The cancer has spread to the lymph nodes above the collar bone (supraclavicular nodes; N3) • The cancer involves axillary lymph nodes and has enlarged the internal mammary lymph nodes (N3) • The cancer has spread to 4 or more axillary lymph nodes, and tiny amounts of cancer are found in internal mammary lymph nodes on a sentinel lymph node biopsy (N3) • The cancer has not spread to distant sites (M0)
IV	Any T, Any N, M1	The cancer can be of any size (any T) and may or may not have spread to nearby lymph nodes (any N). It has spread to distant organs or to lymph nodes far from the breast (M1). The most common sites of spread are the bones, liver, brain, or lungs. Stage IV cancer is advanced disease which is incurable.

Abbreviations: DCIS: ductal carcinoma in situ; TNM: Tumour, Node, Metastases.
Source: AJCC 8th Edition Cancer Staging Manual;[38] American Cancer Society;[40] NCCN Guidelines.[41]

Grade

A further key prognostic factor in breast cancer is tumour grade.[42] Tumour grading is a measure of how abnormal the cancer cells and tissues look under a microscope and provides an indication of how quickly the tumour may grow and spread.[43] Breast cancers are typically classified into Grade 1, Grade 2 or Grade 3 tumours. Notably, lower-grade tumours (i.e., Grade 1) are typically less aggressive and have a better prognosis than higher-grade tumours (i.e., Grade 2 or Grade 3).[44]

Biological risk factors

Finally, there are several biological risk factors that impact disease prognosis and risk of recurrence in EBC such as the presence or absence of certain genetic factors. Genomic tests including Oncotype DX Breast Recurrence Score Test,[45] the Prosigna Breast Cancer Prognostic Gene Signature Assay (formally the PAM50 test),[46] the MammaPrint test,[47] and the EndoPredict test (which gives a EPclin Risk Score) are used to quantify genomic risk factors.[48] Additionally, levels of the antigen Kiel 67 (Ki-67) can be analysed to assess breast cancer proliferation and are considered a prognostic marker for breast cancer patients.[49]

B.1.3.3 Epidemiology

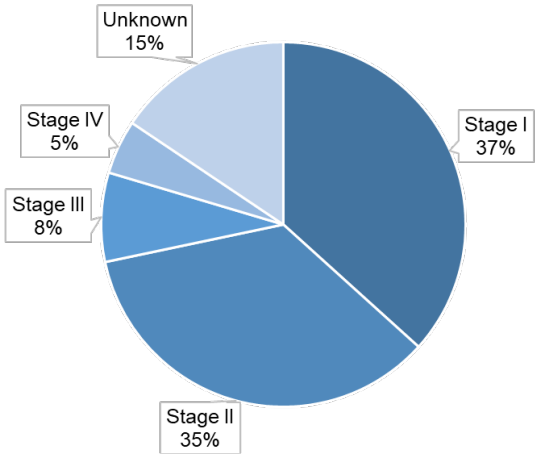
Breast cancer is the most common cancer in the UK, with approximately 56,800 new cases diagnosed every year.[16] It is the fourth most common cause of cancer death in the UK, and the second most common in women, accounting for approximately 11,500 deaths in women and 85 deaths in men every year.[16] Breast cancer incidence is strongly related to age and sex, with 82% of new breast cancer diagnoses in the UK occurring in women aged 50 and older, approximately a quarter of cases in women aged older than 75, and around 1% occurring in males.[50] The incidence rate of breast cancer among post-menopausal women (2.24 per 1,000 person-years) is higher than the incidence rate among pre-menopausal women (1.55 per 1,000 person-years).[51]

Most breast cancer patients are diagnosed with EBC, with 36.7%, 35.0%, 7.9% of breast cancer

patients in England diagnosed with Stage I, Stage II, and Stage III disease, respectively (Figure 3).[18] In contrast, breast cancer that has spread to other parts of the body is classified as advanced or metastatic (Stage IV) disease; approximately 5% of breast cancer cases in England are diagnosed at Stage IV.[18]

As shown in Figure 3, the majority of breast cancer patients in the UK are diagnosed at an early stage, in part due to the understanding of the specific symptoms of breast cancer and the UK's successful breast cancer screening program. However, as the risk of recurrence remains considerable among this patient population (see Section B.1.3.5), more treatment options would be valuable to allow this large population of patients to be treated with effective therapies earlier on, and to prevent disease progression or recurrence.

Figure 3: Proportion of breast cancer cases by stage at diagnosis in England (2021)



Source: Cancer Research UK Early Diagnosis Data Hub.[18]

B.1.3.4 Treatment pathway

Diagnosis

Diagnosis of breast cancer typically comprises a 'triple assessment' with breast examination, imaging (such as mammogram and/or ultrasound scan) and biopsy.[32] Breast biopsies remove a sample of the suspected breast tissue cells. Biopsy samples undergo testing to confirm whether they are cancerous and can subsequently be tested for receptor status to identify the specific subtype (e.g. HR+/HR– or HER2+/HER2–) of breast cancer present.[19]

Current pathway in UK clinical practice

The clinical guideline followed in the UK is NICE Guideline 101 (NG101), which outlines the existing treatment pathway for managing early and locally advanced breast cancer in UK clinical practice.[19] It should be noted that, following approval from the Food and Drug Administration (FDA) in the US, breast cancer clinical guidelines from the National Comprehensive Cancer Network (NCCN; version 5 [2024]) now include the consideration of ribociclib for patients with HR+/HER2– breast cancer in the adjuvant setting,[52] demonstrating the recognised value of ribociclib as a treatment option in this indication.

NG101 recommends a combination of surgery and appropriate systemic therapy ([neo]adjuvant therapy) for all individuals with EBC, unless significant comorbidity precludes surgery.[19] Neoadjuvant therapy refers to treatments given prior to the primary cancer treatment (most

commonly surgery), while adjuvant therapy typically refers to treatments administered after the primary cancer treatment. In this submission, adjuvant therapy refers to treatment administered post-surgical resection of the primary tumour. Figure 4 summarises the treatment pathway for breast cancer recommended by NG101.[19]

Neoadjuvant therapy

Before undergoing surgery, individuals for whom adjuvant therapy is indicated may be offered neoadjuvant chemotherapy to reduce tumour size. For postmenopausal women, if there is no definite indication for neoadjuvant chemotherapy, neoadjuvant ET, which in EBC comprises either tamoxifen or an AI, may instead be considered.[19]

Adjuvant chemotherapy and radiotherapy

Following surgical resection of the primary breast tumour, recommendations for adjuvant therapy should be based on prognostic and predictive factors, as well as the risks and benefits of treatment.[19] Adjuvant chemotherapy may be offered to some patients considered to be at high risk of recurrence, with adjuvant chemotherapy decisions in EBC guided by tumour profiling tests (including EndoPredict, MammaPrint, Oncotype DX and Prosigna).[19, 53] Similarly for some patients, adjuvant radiotherapy may be an option and can include whole breast radiotherapy, partial breast radiotherapy, or post mastectomy radiotherapy.[19]

This submission focuses on adjuvant pharmacotherapy as described below.

Adjuvant pharmacotherapy

Endocrine therapy

ET is the mainstay adjuvant pharmacotherapy option for patients with HR+/HER2– breast cancer and can include either the blocking of ERs or prevention of oestrogen production, targeting the hormone-dependent nature of HR+ breast cancer.[54] The ET regimen recommended is dependent on menopausal status, risk of recurrence, and tolerance to medication. In addition to ET, ovarian function suppression (OFS) should be considered among premenopausal women,[19] and may consist of a gonadotropin-releasing hormone (GnRH) or surgery.

NG101 states that men and premenopausal women should be offered tamoxifen, with additional adjuvant OFS as a consideration for premenopausal women. However, in UK clinical practice, feedback from UK clinical experts indicates that premenopausal women are prescribed both tamoxifen (with or without OFS) and AIs (with OFS) (see Appendix Q.2). Notably, AIs are considered more effective than tamoxifen in reducing disease recurrence (see Appendix M.1). Postmenopausal women at medium or high risk of recurrence should be offered an AI, as the initial adjuvant ET, while postmenopausal women at low risk of recurrence, or for whom AIs are not tolerated or contraindicated, should be offered tamoxifen.[19] Extended adjuvant therapy (for more than five years) with an AI should be offered to postmenopausal women at increased risk of recurrence who have been taking tamoxifen for 2 to 5 years.[19]

Finally, bisphosphonates, a group of drugs usually used to prevent bone density loss, may also be offered as add-on adjuvant therapy to postmenopausal women with node-positive breast cancer, or considered for postmenopausal women with node-negative breast cancer at high risk of recurrence.[19]

Abemaciclib

The CDK4/6 inhibitor abemaciclib received a positive recommendation from NICE in 2022 (TA810) as an additional adjuvant therapy option in combination with ET for a subgroup of patients with node-positive HR+/HER2– EBC at high risk of recurrence.[6] As discussed in Section B.1.1, abemaciclib represents a relevant comparator in Population 4 (node-positive high-risk eligible for abemaciclib), which is defined as per the abemaciclib NICE TAG (TA810) as node-positive HR+/HER2– EBC with: pathological tumour involvement in ≥4 ALNs, or pathological tumour involvement in 1–3 ALNs as well as at least one of the following indicators of high disease recurrence risk; Grade 3 disease or primary tumour size ≥5 cm, irrespective of Ki-67 status.[6]

Positioning of ribociclib

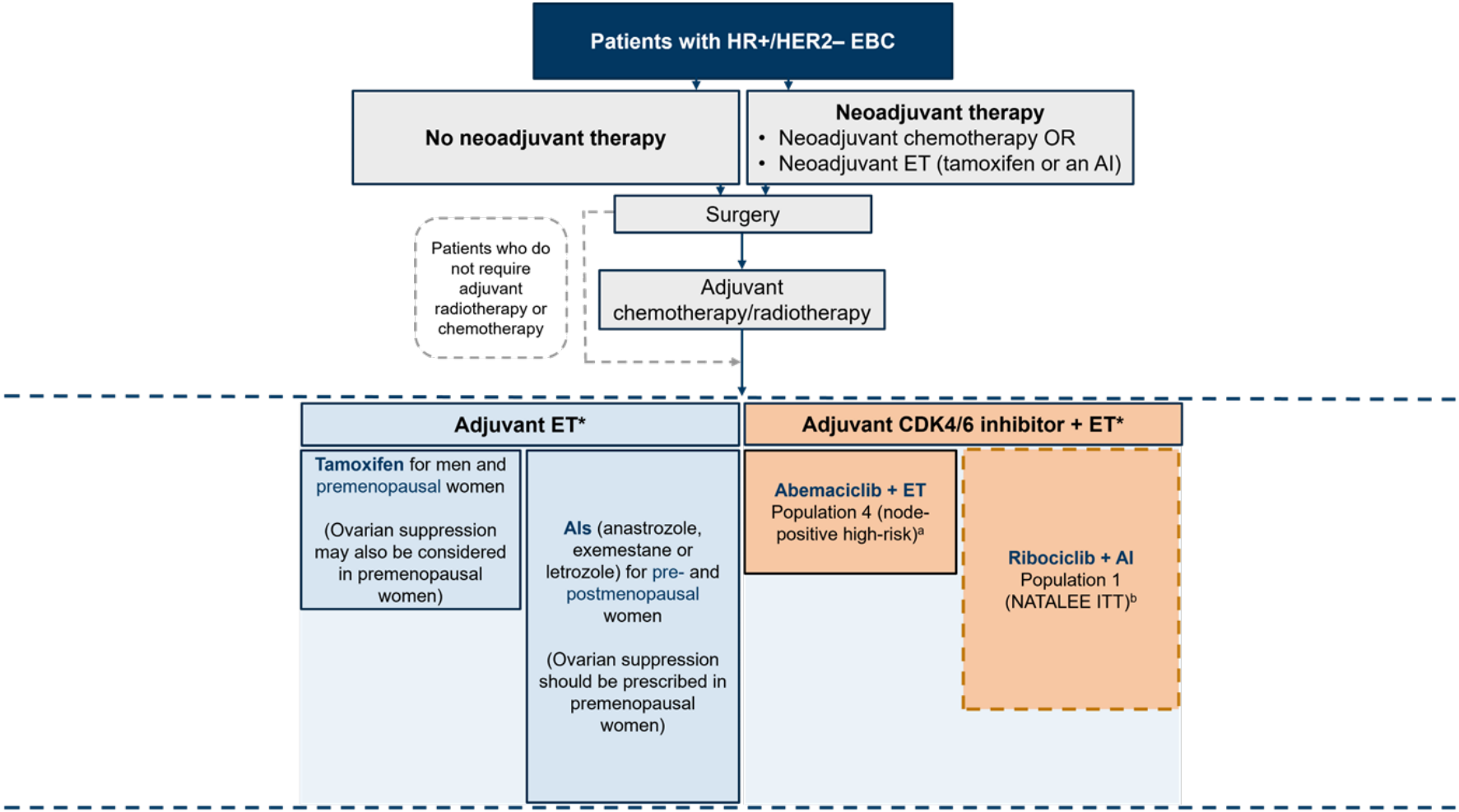
Figure 4 summarises the treatment pathway for EBC recommended by NG101 and the anticipated positioning of ribociclib in the pathway.[19]

In the base case of this submission, ribociclib plus AI is being positioned a new treatment option for patients in the full population of HR+/HER2– EBC at high risk of recurrence (Population 1 [NATALEE ITT]).

Subgroup analyses are also being considered in the following three populations:

- Population 2 (NATALEE node-positive high-risk), defined in Section B.1.1, where the relevant comparator is ET
- Population 3 (NATALEE node-negative high-risk), defined in Section B.1.1, where the relevant comparator is ET
- Population 4 (node-positive high-risk eligible for abemaciclib), defined in Section B.1.1, where the relevant comparators are abemaciclib plus ET and ET.

Figure 4: Current treatment pathway for HR+/HER2– EBC in the UK, and the relative positioning of ribociclib



Footnotes: * Bisphosphonates may be prescribed as an add-on treatment for postmenopausal women with sufficient risk of recurrence. [a] "High risk of recurrence" as defined per TA810 recommendation.[6] [b] "High risk of recurrence" as defined per NATALEE eligibility criteria.[2]
Abbreviations: AI: aromatase inhibitor; CDK4/6: cyclin dependent kinase 4 and 6; EBC: early breast cancer; ET: endocrine therapy; HER2: human epidermal growth factor receptor 2; HR: hormone receptor.
Source: NICE Guideline NG101.[19]

B.1.3.5 Disease burden

Breast cancer recurrence and survival outcomes

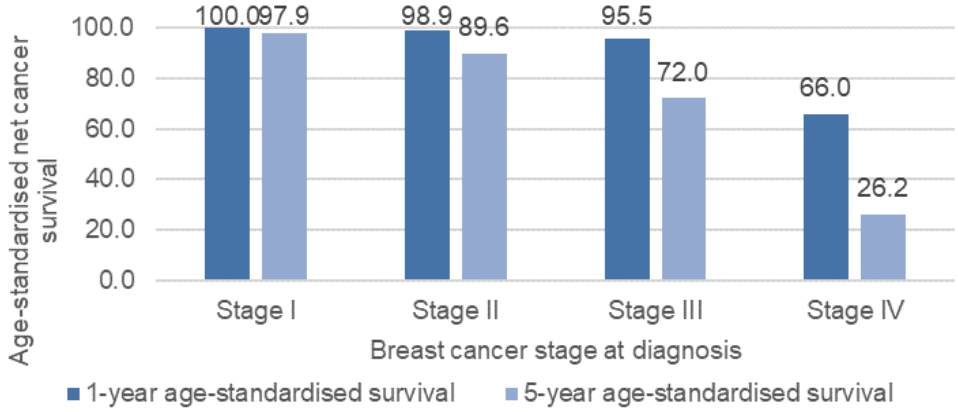
Disease recurrence is one of the most important factors associated with the substantial mortality burden of breast cancer and the type of recurrence is particularly important, as it determines whether the disease can be considered curable or incurable. Disease recurrence can be categorised as follows:[55]

- Local recurrence: When the cancer returns to the same part of the breast as the initial diagnosis
- Regional recurrence: When the breast cancer is found in nearby lymph nodes and/or the chest wall
- Distant recurrence: Also referred to as advanced or metastatic breast cancer; this occurs when breast cancer cells (including micro-metastases [small clusters of tumour cells that are too small to be detectable via imaging]) travel to other parts of the body through the lymphatic system or bloodstream. Common sites of breast cancer metastasis include the bones, liver and lungs. Distant recurrence is the primary cause of death in patients with EBC.[56]

It is important to note that recurrent disease is likely to progress into advanced or metastatic disease (either locally advanced disease that cannot be completely removed by surgery, or advanced disease that has spread to other areas of the body).[56] Advanced or metastatic (Stage IV) breast cancer cannot be removed entirely by surgery and is therefore considered incurable. Patients living with advanced or metastatic breast cancer report reduced health-related quality of life (HRQoL), increased symptom burden, and have a considerably poorer prognosis and increased risk of death from breast cancer, than patients with earlier-stage disease.[20, 57]

Notably, for patients diagnosed with Stage I, II and III breast cancer (i.e., EBC), the 5-year age-standardised survival rates in England are 97.9%, 89.6%, and 72.0% respectively, while for Stage IV cancer patients, the 5-year age-standardised survival rate drops to 26.2% (Figure 5). This reiterates the importance of providing early treatment options for EBC that have the potential to successfully prevent breast cancer progression and recurrence, given the drastically poorer prognosis and increased risk of death from breast cancer associated with later stage disease.

Figure 5: Five-year age-standardised net breast cancer survival for adults (aged 15 to 99 years) diagnosed between 2013 and 2017 in England



Source: Office for National Statistics.[58]

Given the substantially poorer prognosis for patients with advanced or metastatic breast cancer compared with those diagnosed at an earlier stage, the goal of treatment for EBC is of curative intent and aims to prevent disease recurrence.[59] However, despite the long-standing availability of adjuvant ET, the risk of breast cancer recurrence still persists; the 20-year risk of disease recurrence across all HR+/HER2– EBC patients ranges from 10–41% dependent on anatomical and biological disease risk factors.[20] Notably, more than 50% of breast cancer recurrences occur more than 5 years after diagnosis.[21]

As discussed in Section B.1.3.2, in addition to tumour stage, there are several other factors that affect the risk of disease recurrence, including nodal involvement, grade and genomic risk factors. A large retrospective real-world study of patients with HR+/HER2− EBC (N=7,564) demonstrated that all patients with EBC with high-risk features (as defined by the NATALEE ITT eligibility criteria [see Section B.1.1])[2] had a significant risk of overall recurrence and distant recurrence.[23] At seven years, the risk of recurrence among patients with node-negative (N0) disease with additional high risk factors and patients with N1 disease was similar; the overall risk of recurrence was 16.9% (95% CI: 13.3, 21.3%) and 17.1% (95% CI: 14.7, 19.8%), respectively, while the risk of distance recurrence was 13.6% (95% CI: 10.3, 17.8%) and 13.7% (95% CI: 11.5, 16.2%), respectively.[23] For patients with high-risk N2+ disease, the overall risk of recurrence was even higher at 43.7% (95% CI: 37.9, 50.0), while the risk of distance recurrence was 40.1% (95% CI: 34.4, 46.4%).[23] This demonstrates the influence of several disease characteristics, such as tumour stage, grade and genomic risk factors on the overall risk of recurrence and, in turn, patient prognosis.

Given all recurrences (including local, regional and distant) are associated with a significant health burden,[60] in addition to distant recurrences generally being incurable and eventually leading to death due to breast cancer, there is a distinct clinical unmet need for new, more effective treatment options to prevent disease recurrence in patients with HR+/HER2– EBC at high risk of recurrence. This includes a particular unmet need for patients with node-negative HR+/HER2– EBC at high risk of recurrence (representing 23% of all HR+/HER2– EBC patients at high risk of recurrence) and patients with N1 disease without additional specific anatomical risk factors (representing 35% of all HR+/HER2– EBC patients at high risk of recurrence)[7] for whom adjuvant therapy in UK clinical practice is restricted to ET (with or without add-on adjuvant treatment with bisphosphonates for postmenopausal women) given they are not eligible for abemaciclib plus ET.[19]

Treatment adherence

An additional burden of EBC relates to the adherence of patients to ET. Adherence to adjuvant ET is known to be suboptimal within clinical practice and is influenced by multiple factors, including socioeconomic, health system-related, patient-related, treatment-related, and condition-related factors.[61-64] Notably, treatment-related factors are the most commonly-reported barrier to ET adherence.[65] Symptomatic ET-related adverse events (AEs), such as diarrhoea and fatigue, detrimentally impact patients' HRQoL, and decrease treatment adherence. Patients receiving ET may also experience an abrupt onset of ET-induced menopausal symptoms (including hot flushes, night sweats, arthralgia and sexual dysfunction) which also negatively impact patients' HRQoL and in turn, further compromise adherence to ET.[66, 67]

HRQoL burden

Breast cancer is associated with a considerable burden on the HRQoL of patients and their

caregivers. Compared with the general population, individuals with breast cancer experience a reduction in HRQoL which continues to decline as breast cancer progresses.[68] HRQoL of breast cancer patients is negatively associated with later-stage disease at diagnosis and also with the experience of any recent disease recurrence or metastasis,[57] reiterating the need to prevent disease relapse. Poorer HRQoL among breast cancer patients can be attributed to symptoms of the disease which worsen with disease progression, treatment-related AEs such as diarrhoea and fatigue, psychological effects, and reductions in patients' ability to work and manage daily tasks.[63, 69]

Moreover, fear of disease recurrence detrimentally impacts psychological wellbeing and overall HRQoL long-term.[22] A large UK-based cohort study (1988–2018) comparing women diagnosed with breast cancer (N=57,571) to those with no prior cancer diagnosis (N=230,067) found a 33% increased risk of anxiety and a 35% increased risk of depression in breast cancer patients, persisting for 2- and 4- years post-diagnosis, respectively.[70] Depression and anxiety are also more prevalent among women diagnosed with recurrent breast cancer; an NHS-based study of 202 women diagnosed with EBC between May 1991 and July 1994 identified that 45% of women had an episode of depression, anxiety, or both, in the three months following a diagnosis of recurrent breast cancer, compared with 36% of women following an initial breast cancer diagnosis.[71]

Caregivers of patients with breast cancer are also detrimentally impacted by the effects of the disease; they face physical, emotional, and financial challenges, all of which compromise caregivers' HRQoL.[72, 73] As such, preventing disease recurrence and progression to later stage disease is vital to improve HRQoL and bring confidence to patients, caregivers, and families to know that they have an improved likelihood of remaining free of cancer for longer. There is therefore a critical a need for new treatment options for EBC patients which reduce the risk of recurrence, and as such, reduce the associated negative effects of advanced or metastatic disease, such as disease symptoms, psychological effects, and impact on caregivers.

Economic burden

Finally, in addition to the burden on patients and caregivers, breast cancer imparts a significant burden on the UK economy and NHS resources. According to a study conducted in 2012 by the University of Oxford, breast cancer costs the NHS an estimated £1.5 billion every year.[74] This represents approximately 10% of the total annual cost of all cancers to the UK economy.[74] Costs can be direct, for example through healthcare resource utilisation (e.g. treatment costs, clinical tests and procedures, and medical visits), or indirect, for example through caregiver and patient productivity loss.[75, 76]

The introduction of a more effective, well-tolerated treatment that minimises the impact of breast cancer on patient and caregiver productivity would benefit not only breast cancer patients and their caregivers, but may reduce the substantial financial burden that breast cancer currently imparts on the NHS and UK economy.

B.1.3.6 Unmet need

As highlighted in Section B.1.3.3, approximately 56,800 new cases of breast cancer are diagnosed in the UK every year.[16] The vast majority of these are diagnosed as early-stage disease,[18] and 68% of cases are HR+/HER2–.[17]

Current adjuvant therapy options for patients with HR+/HER2– EBC are limited to ET (with or

without add-on bisphosphonates) or abemaciclib plus ET (for patients in Population 4 only [node-positive high-risk eligible for abemaciclib], as defined in Section B.1.1) (Figure 4). Notably, patients treated with ET remain at a substantial risk of disease recurrence,[20] and this risk persists long term (see Section B.1.3.5).[21]

monarchE, the pivotal trial for abemaciclib plus ET demonstrated that the addition of abemaciclib to ET reduced the risk of disease recurrence compared with ET for patients in Population 4 (node-positive high-risk eligible for abemaciclib).[77] However, a significant proportion of HR+/HER2– EBC patients at high risk of recurrence (Population 1 [NATALEE ITT] as defined by the ITT NATALEE eligibility criteria [see Section B.1.1]) are not eligible for abemaciclib plus ET (see Table 4 and Figure 1).

Approximately 23% of all HR+/HER2– EBC patients at high risk of recurrence have node-negative disease and are not eligible for abemaciclib plus ET;[7] the short-term (7-year) cumulative risk of invasive disease recurrence among these patients is substantial at 25.7%,[23, 24] while the incidence of overall recurrence is 16.9%.[24] Additionally, approximately 35% of all HR+/HER2– EBC patients at high risk of recurrence have N1 disease without additional specific risk factors (as defined by TA810) and are therefore also not eligible for abemaciclib plus ET.[7] Again, the risk of recurrence in these patients is significant, with a 7-year incidence of overall recurrence of 17.1%.[24]

Table 4: The population included in monarchE Cohort 1 (abemaciclib plus ET), compared with the population included in NATALEE (ribociclib plus AI)

AJCC anatomical staging	TN (M0)	NATALEE	monarchE Cohort 1
Stage IIA	T0N1	Included	Only if grade 3
	T1N1	Included	
	T2N0	Only if grade 3, or grade 2 with Ki67 ≥20%, or high genomic risk	Not included
Stage IIB	T2N1	Included	Only if grade 3
	T3N0	Included	Not included
Stage IIIA	T0N2	Included	Included
	T1N2	Included	Included
	T2N2	Included	Included
	T3N1	Included	Included
	T3N2	Included	Included
Stage IIIB	T4N0	Included	Included
	T4N1	Included	Only if tumour size ≥5cm or grade 3
	T4N2	Included	Included
Stage IIIC	Any TN3	Included	Included

Footnotes: Note that the monarchE Cohort 1 population indicates the population eligible for abemaciclib plus ET based on NICE TA810, while the NATALEE population represents the population that would be eligible for ribociclib plus AI, if it were to receive a positive recommendation from NICE in this indication.
Abbreviations: AJCC: American Joint Committee on Cancer; Ki-67: Antigen Kiel 67; N: regional lymph nodes; T: tumour.
Source: NICE TA810;[2] Toi *et al*. (2022);[78] Novartis Data on File: NATALEE Protocol.[2]

There is a clear unmet need for an effective treatment option that reduces the risk of disease recurrence for patients in the full population of HR+/HER2– EBC at high risk of recurrence (Population 1 [NATALEE ITT]), including patients who are not eligible for abemaciclib plus ET.

Additionally, abemaciclib has a different safety profile in terms of symptomatic AEs compared with ribociclib, which clinicians and patients may consider when choosing their EBC treatment. Safety analyses of the monarchE and NATALEE trials indicate that symptomatic AEs such as diarrhoea and fatigue (which are known to be of particular concern for patients' quality of life) are more frequently reported by patients receiving abemaciclib plus ET than those receiving ribociclib plus AI. Indeed, diarrhoea was experienced by 83.5% patients in monarchE, compared with 14.6% of patients in NATALEE.[79] As such, despite the availability of abemaciclib plus ET for patients in Population 4 (node-positive high-risk eligible for abemaciclib), an unmet need remains for a choice of therapeutic options that reduce the risk of patients' disease recurring or progressing into incurable advanced or metastatic disease, with good tolerability to maintain patients' quality of life.

Finally, it is the Company's understanding from multiple clinical experts that some patients undergo an additional surgical procedure (axillary lymph node dissection [ALND]) in order to identify additional positive axillary lymph nodes that would qualify them for treatment with adjuvant abemaciclib plus ET. Specifically, these patients are those with 1-2 positive lymph nodes without any additional high-risk characteristics (tumour size / grade) who would not typically undergo ALND (patients with 3 positive lymph nodes would typically undergo ALND regardless). ALND is associated with significant morbidity in the form of increased rates of lymphedema, pain, infection, numbness and weakness. There is therefore an unmet need for a new treatment option to be available for patients with 1-3 positive ALNs, regardless of the presence of additional high-risk characteristics, to help reduce the need for additional ALND surgery.[80]

Ribociclib

Ribociclib is an orally administered, potent, and highly selective small-molecular inhibitor of CDK4 and CDK6. CDK4/6s are responsible for promoting phosphorylation of the retinoblastoma protein (a tumour suppressor protein that blocks cell cycle progression), ultimately allowing cells to continue through the cycle and promoting cell proliferation.[81] Importantly, imbalance of the cyclin D–CDK pathway is associated with a proliferative phenotype in cancer cells.[10]

Ribociclib blocks the phosphorylation of retinoblastoma proteins, preventing the progression of the cell from the growth (G1) phase to the DNA synthesis phase (S). By inhibiting DNA synthesis, CDK4/6 inhibition leads to cell senescence, where cells are in a state of irreversible cell cycle arrest and are no longer responsive to growth-promoting stimuli.[82] Notably, CDK4/6 inhibition has been shown to block cell cycle progression in endocrine-resistant breast cancer cells.[12]

Preclinical data have identified that ribociclib selectively inhibits CDK4 (the active target in breast cancer) preferentially over CDK6,[83] causing cell cycle arrest which is important for the treatment of breast cancer.[84] Ribociclib also achieves high plasma drug concentrations for binding and acting on tumour cells; compared with other CDK4/6 inhibitors, ribociclib achieves highest time on-target CDK4 inhibition.[84, 85]

Ribociclib has already demonstrated its efficacy and favourable long-term safety in advanced or metastatic breast cancer. Ribociclib is the only CDK4/6 inhibitor to have a significant and consistent OS advantage in three large Phase III trials in HR+, HER2– advanced or metastatic

breast cancer in pre- and post-menopausal patients, with different sites of metastases, different ET combinations, regardless of ET resistance, and in different lines of therapy.[25-27] AEs associated with ribociclib are mostly asymptomatic (e.g. laboratory abnormalities) and decrease over time.[86, 87] This is particularly important for patients with EBC who tend to have low rates of treatment adherence,[61] often due to unpleasant treatment-related factors.[65] Additionally, based on an anchored matching-adjusted treatment comparison (MAIC) comparing ribociclib plus AI vs abemaciclib plus AI in the advanced or metastatic disease setting, treatment with ribociclib plus AI (compared with treatment with abemaciclib plus AI) is anticipated to result in improved patient HRQoL.[88]

Ribociclib is prescribed in the advanced or metastatic breast cancer setting at a dose of 600 mg; if it were to receive a positive recommendation in the EBC setting, ribociclib would be prescribed at a lower dose of 400 mg for a total of three years in line with the dosing in the NATALEE trial.[1] This dosing regime was chosen in order to optimise efficacy and protect against short- and long-term recurrence while improving tolerability in this patient population as the treatment duration of ribociclib in EBC covers the initial peak interval of annualised hazard for recurrence or death between Years 1–3 following the initiation of ET. Clinical effectiveness results from NATALEE, the pivotal trial for ribociclib in HR+/HER2– EBC at high risk of recurrence are presented in Section B.2.5.

For HR+/HER2– EBC patients at high risk of recurrence (but not eligible for abemaciclib plus ET), adjuvant therapy is currently limited to ET (with or without add-on bisphosphonate therapy). Ribociclib plus AI will therefore provide an additional treatment option that is expected to reduce the risk of recurrence and improve survival rates compared to treatment with ET. For patients in Population 4 (node-positive high-risk eligible for abemaciclib), ribociclib plus AI will provide an alternative, well-tolerated treatment option that has the potential to provide prolonged protection from breast cancer recurrence.

B.1.4 Equality considerations

The marketing authorisation extension for ribociclib in EBC is anticipated to cover both women and men, and it is not expected that this appraisal will exclude any people protected by equality legislation, nor is it expected to lead to a recommendation that would have a different impact on people protected by equality legislation than on the wider population. Similarly, it is not expected that this appraisal will lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

B.2 Clinical effectiveness

Summary

- The pivotal trial for ribociclib plus AI in the indication relevant to this submission is the Phase III NATALEE trial (NCT03701334).[89] NATALEE compared ribociclib (400 mg) plus AI (n=2,549) with AI (n=2,552), in patients with HR+/ HER2– EBC at high risk of recurrence (N=5,101; Population 1 [NATALEE ITT]).
- The primary endpoint of NATALEE was iDFS. Secondary endpoints included recurrence-free survival (RFS), distant disease-free survival (DDFS), OS, patient-reported outcomes (PROs), and safety outcomes.
- This submission predominantly presents data from the latest available data cut of NATALEE from April 2024 (data cut-off: 29th April 2024) as well as the pre-planned analysis of iDFS (PA) (data cut-off: 21st July 2023) and the IA3 (data cut-off: 11th January 2023).

Summary of the clinical effectiveness evidence vs AI in Population 1 (NATALEE ITT)

- At the PA (data cut-off: 21st July 2023; median follow-up: 40.3 months) and the April 2024 data cut (data cut-off: 29th April 2024; median follow-up: [redacted] months), treatment with ribociclib plus AI was associated with a statistically significant improvement in iDFS compared with AI.
- At the PA (July 2023), ribociclib plus AI reduced the risk of developing invasive disease by 25.1% compared with AI (hazard ratio [HR]: 0.749; 95% CI: 0.628, 0.892, [redacted]). At the April 2024 data cut, an even greater statistically significant improvement in iDFS was observed for ribociclib plus AI vs AI. Ribociclib plus AI reduced the risk of an iDFS event by 28.5% (HR: 0.715; 95% CI: 0.609, 0.840, one-sided stratified log-rank test p-value=0.0001), with 4-year iDFS rates of 88.5% (95% CI: [redacted]) vs 83.6% (95% CI: [redacted]) in the ribociclib plus AI and AI arms, respectively. Overall, the iDFS improvement was consistent across all pre-specified subgroups including menopausal status and nodal status.
- Results from the secondary efficacy endpoint analyses further reaffirmed the robustness of the iDFS results. At the April 2024 data cut, RFS results showed that ribociclib plus AI resulted in a [redacted] relative reduction in the risk of a patient experiencing disease recurrence vs AI [redacted] and DDFS results showed a 28.5% relative reduction in the risk of a distant recurrence among patients in the ribociclib plus AI arm (HR: 0.715; 95% CI: 0.604, 0.847, one-sided stratified log-rank test p-value<0.0001) compared with the AI arm.
- The OS data at the April 2024 data cut demonstrated a trend in OS in favour of ribociclib plus AI compared with AI (HR: 0.827; 95% CI: 0.636, 1.074, one-sided stratified log-rank test p=0.0766). iDFS and DDFS have been used as surrogates for OS in previous breast cancer studies,[90] and observed improvements in these endpoints are anticipated, in the long term, to translate into improvements in OS.
- PRO data were only collected at IA3 (data cut: 11th January 2023). At IA3 (January 2023; median follow-up: 34.0 months), there were [redacted] in European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-

Core 30 (EORTC QLQ-C30) scores from baseline through to end of treatment, and all other PROs indicated [redacted] in predicted values between treatment arms; these results therefore show the clinical benefit of ribociclib was achieved without a reduction in patients' HRQoL.

Summary of the safety evidence vs AI in Population 1 (NATALEE ITT)

- Overall, safety results from the April 2024 data cut of NATALEE showed that ribociclib plus AI is associated with a predictable and manageable safety profile. No new safety signals or safety concerns were identified; ribociclib-related AEs are well characterised from the advanced or metastatic breast cancer indication, manageable with appropriate intervention, and generally reversible upon treatment adjustment.
- At the April 2024 data cut, the most common treatment-emergent adverse events (TEAEs; all grades, irrespective of causality) in the ribociclib plus AI arm were [redacted] and [redacted]. As might be expected, higher incidences of AEs leading to discontinuation of study treatment occurred in the ribociclib plus AI arm in comparison to the AI only arm [redacted].

Summary of the clinical evidence for ribociclib plus AI vs AI in Population 2 (NATALEE node-positive high-risk) and Population 3 (NATALEE node-negative high-risk)

- At the PA (July 2023), ribociclib plus AI vs AI reduced the relative risk of developing invasive disease by 24.1% (HR: 0.759; 95% CI: 0.631, 0.912) and 27.7% (HR: 0.723; 95% CI: 0.412, 1.268), in Population 2 (NATALEE node-positive high-risk) and Population 3 (NATALEE node-negative high-risk), respectively.
- At the April 2024 data cut, the iDFS HR for ribociclib plus AI vs AI had improved to 0.731 (95% CI: 0.617, 0.866) in Population 2 (NATALEE node-positive high-risk), representing a 26.9% relative reduction in the risk of an iDFS event, and to 0.666 (95% CI: 0.397, 1.118) in Population 3 (NATALEE node-negative high-risk), representing a 33.4% relative reduction in the risk of an iDFS event.
- The results across Populations 2 and 3 (NATALEE node-positive high-risk and node-negative high-risk) were similar to the 28.5% relative risk reduction of an iDFS event observed in the Population 1 (NATALEE ITT) at the April 2024 data cut.

Summary of the clinical and safety evidence vs abemaciclib plus ET and ET in Population 4 (node-positive high-risk eligible for abemaciclib)

- Given the lack of head-to-head data between ribociclib plus AI and abemaciclib plus ET and ET in Population 4 (node-positive high-risk eligible for abemaciclib), a MAIC was performed to enable their comparison.
- Patients in the NATALEE trial were selected to match the key eligibility criteria for Cohort 1 of the monarchE trial (for abemaciclib plus ET). In the primary MAIC analysis, patients were matched for all possible baseline characteristics. Comparisons of iDFS and OS were conducted between ribociclib plus AI and abemaciclib plus ET and ET via Cox regressions using both the weighted and unweighted samples of patients from the NATALEE trial. The AI arm of the NATALEE trial was used to inform the efficacy of ET.
- In the primary MAIC analysis of ribociclib plus AI vs abemaciclib plus ET in Population 4 (node-positive high-risk eligible for abemaciclib), there was no statistically significant

difference in treatment effect between ribociclib plus AI and abemaciclib plus ET across both efficacy endpoints explored [redacted] No significant differences were also observed in the sensitivity analysis that matched for an alternative set of baseline characteristics (see Appendix D).

- In the primary MAIC analysis of ribociclib plus AI vs ET in Population 4 (node-positive high-risk eligible for abemaciclib), ribociclib plus AI statistically significantly reduced the relative risk of an iDFS event [redacted]), and indicated an improvement in OS with ribociclib plus AI over ET [redacted] although the difference was not statistically significant. The sensitivity analysis adjusting for an alternative set of characteristics was consistent with the primary MAIC analysis (see Appendix D).
- The primary MAIC analysis of TEAEs between ribociclib plus AI and abemaciclib plus ET in Population 4 (node-positive high-risk eligible for abemaciclib) demonstrated a statistically significantly reduced odds of diarrhoea, leukopenia, and lymphopenia but a statistically significantly increased odds of ALT increase, and neutropenia for ribociclib plus AI vs abemaciclib plus ET.
- Results from NATALEE and from the MAIC analysis show ribociclib plus AI to be associated with statistically significantly increased efficacy in terms of iDFS and OS vs ET in Population 1 (NATALEE ITT), Population 2 (NATALEE node-positive high-risk) and Population 3 (NATALEE node-negative high-risk). Additionally, results from the primary MAIC analysis in Population 4 (node-positive high-risk eligible for abemaciclib) indicated no statistically significant difference in efficacy between ribociclib plus AI and abemaciclib plus ET, suggesting that ribociclib plus AI provides an alternative treatment option in this population.

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted in March 2023 (original SLR), and subsequently updated in October 2023 (clinical SLR update 1) and June 2024 (clinical SLR update 2) to identify all relevant clinical evidence for the efficacy and safety of ribociclib plus AI and other relevant treatment options for patients with HR+/HER2– EBC.

Overall, 195 records, reporting on 52 unique studies, were identified in the SLR. Of these, one study was identified for ribociclib plus AI (NATALEE), one study for abemaciclib plus ET (monarchE), and 46 studies for ET. The remaining studies were for palbociclib and everolimus, which are not relevant to the decision problem. Full details of the SLR search strategy, study selection process, and results are presented in Appendix D.

As the only study reporting clinical evidence for the efficacy and safety of ribociclib plus AI in patients with HR+/HER2– EBC, NATALEE forms the pivotal clinical evidence base for ribociclib plus AI in this submission and is described in detail in the following sections.

B.2.2 List of relevant clinical effectiveness evidence

An overview of the NATALEE trial is provided below in Table 5.

Table 5: Clinical effectiveness evidence: NATALEE

Study	NATALEE (NCT03701334)
Study design	Global, Phase III, multicentre, parallel assignment, randomised, open-label trial
Population	Pre- and postmenopausal women and men with HR+/HER2– EBC, with an AJCC 8th edition Anatomic Stage Group III, IIB or a subset of Stage IIA cases after adequate surgical resection, radiotherapy (if indicated), adjuvant or neoadjuvant chemotherapy (if indicated), and who were deemed to be eligible for adjuvant ET for at least 60 months from the date of randomisation
Intervention(s)	Ribociclib (400 mg orally once daily on days 1 to 21 of a 28-day cycle) for 36 months (approximately 39 cycles) since the randomisation date and AI[a] (letrozole or anastrozole [in combination with goserelin for premenopausal women and men]) for 60 months
Comparator(s)	AI (2.5 mg letrozole daily or 1 mg anastrozole daily [in combination with 3.6 mg goserelin once every 28 days for premenopausal women and men]) for 60 months
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem	**Primary endpoint:** iDFS **Secondary endpoints:** RFS, DDFS, OS, PROs, and safety outcomes
All other reported outcomes	**Secondary endpoints:** Pharmacokinetics **Exploratory endpoints:** Distant recurrence-free survival;[b] locoregional recurrence-free survival,[c] use of subsequent anti-neoplastic therapy,[c] healthcare resource utilisation,[c] prognostic and predictive biomarkers of treatment with ribociclib plus AI,[c] potential molecular mechanisms of resistance to treatment with ribociclib plus AI,[c] and role of ctDNA/ctRNA for their suitability to monitor and predict disease recurrence[c]

Footnotes: [a] Please note that in the NATALEE protocol and CSRs, the terminology "ET" is used. As only AI therapies were received in the NATALEE trial, the "ET" component of the intervention and comparator arm is referred to as AI from hereafter. [b] Explored at the April 2024 data cut. [c] Results for these endpoints are not presented in this submission but can be found in the NATALEE CSRs.
Abbreviations: AI: aromatase inhibitor; AJCC: American Joint Committee on Cancer; DDFS: distant disease-free survival; EBC: early breast cancer; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; iDFS: invasive disease-free survival; OS: overall survival; PRO: patient-reported outcomes; RFS: recurrence-free survival.
Source: Novartis Data on File: NATALEE Protocol.[2]

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

B.2.3.1 Study design

NATALEE is an ongoing Phase III, multicentre, randomised, open-label study designed to evaluate the efficacy and safety of ribociclib plus AI vs AI in pre- and postmenopausal women

and men with HR+/HER2–, Stage IIA–III EBC at high risk of recurrence (Population 1 [NATALEE ITT]). As described in Section B.1, “at high risk of recurrence” is defined in the NATALEE trial inclusion criteria, as adult patients with HR+/HER2– EBC and:

- Anatomical Stage IIA
  - N0 with either:
    - Grade 3, or
    - Grade 2, with any of the following criteria: Ki67 ≥20%, Oncotype DX, Breast Recurrence Score ≥26, Prosigna/PAM50 categorised as high risk, MammaPrint categorised as high risk or EndoPredict EPclin Risk Score categorised as high risk
  - N1
- Anatomical Stage IIB
  - N0 or N1
- Anatomical Stage III
  - N0, N1, N2 or N3

Using an Interactive Response Technology system (IRT), 5,101 eligible patients were randomised in a 1:1 ratio to either the investigational arm (ribociclib plus AI; n=2,549) or the control arm (AI; n=2,552) using menopausal status, AJCC 8th edition Anatomic Stage Group, previous exposure to chemotherapy, and geographical region as stratification factors. The enrollment of patients with Stage II disease was capped at 40%, in order to allow for a better representation of Stage II and III patients in the trial.

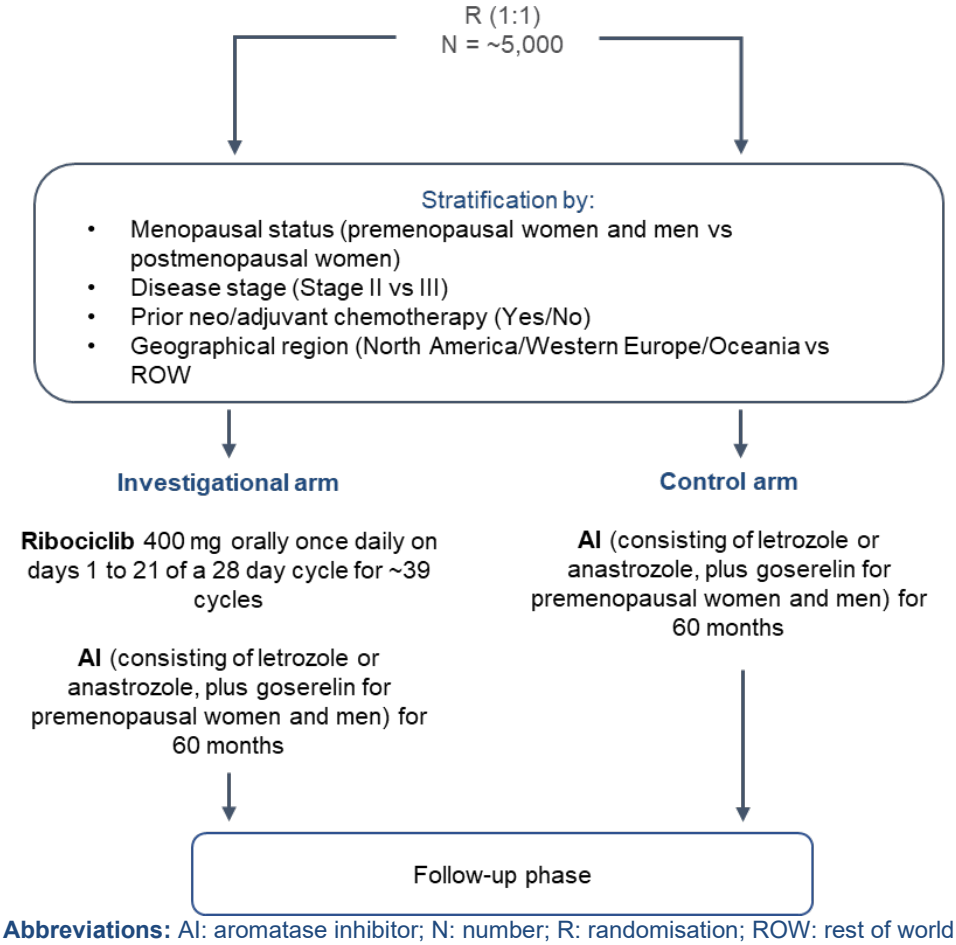
An overview of the NATALEE study design is presented in Figure 6. Starting from Cycle 1 Day 1 (C1D1), patients randomly assigned to the investigational arm (ribociclib plus AI) received ribociclib 400 mg orally once daily on day 1 to 21 of a 28-day cycle for ~39 cycles and either AI consisting of letrozole (2.5 mg once daily continuously) or anastrozole (1 mg once daily continuously) for 60 months. Premenopausal women and men also received goserelin 3.6 mg subcutaneously once every 4 weeks for 60 months. Patients in the control arm (AI) received the same AI as in the investigational arm, also for a duration of 60 months.

Follow-up visits

Trial visits were scheduled at the following stages: screening, randomisation, during treatment, 30 days post discontinuation of ribociclib (30-day Safety Follow-up visit), 15 days after discontinuing all trial treatments (End of Treatment visit), 30 days after discontinuing all trial treatments, and during the follow-up phase.

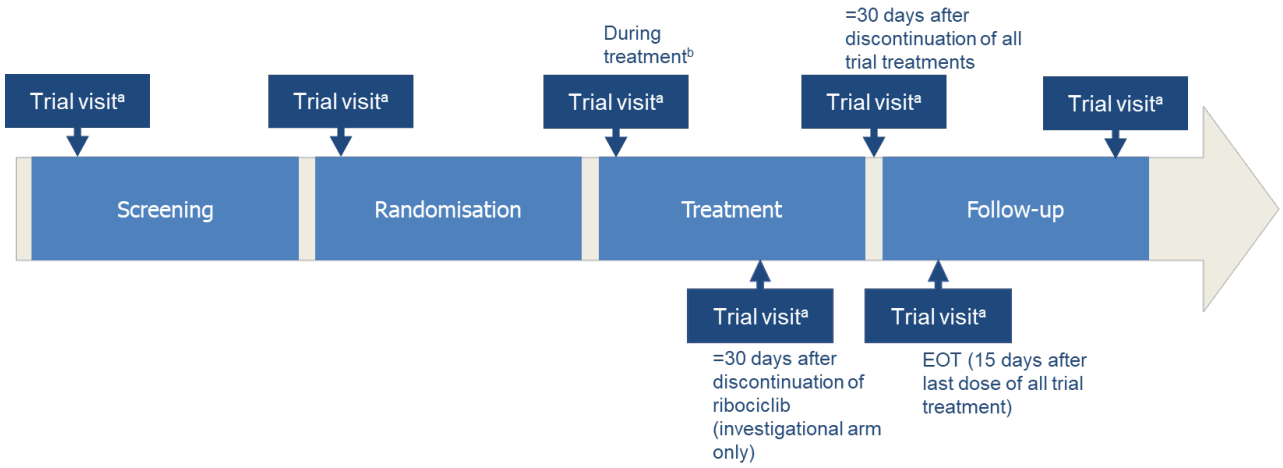
An overview of the NATALEE trial visits and assessments is presented in Figure 7.

Figure 6: Overview of the NATALEE study design



Abbreviations: AI: aromatase inhibitor; N: number; R: randomisation; ROW: rest of world.
Source: Adapted from Novartis Data on File: NATALEE Protocol.[2]

Figure 7: NATALEE trial visits and assessments



Footnotes: [a] For all visits, a ±3 day window was permitted for the applicable assessments (except for ECGs required on Cycle 1 Day 1 [C1D1]), to take into account scheduling issues.
[b] Trial visits were scheduled on day 1 and day 15 for the first two treatment cycles, then on day 1 for cycles 3–6, followed by one visit every third cycle for day 1 of cycle 7.
Abbreviations: ECG: electrocardiogram; EOT: end of treatment.
Source: Adapted from Slamon *et al.* (2023).[91]

An overview of the methodology of NATALEE is presented in Table 6 below.

Table 6: Overview of methodology for NATALEE

Methodology	Summary
Location	NATALEE was an international, multicentre trial conducted in 387 centres across 20 countries: Argentina, Australia, Austria, Belgium, Brazil, Canada, China, France, Germany, Hungary, Ireland, Italy, Republic of Korea, Poland, Romania, Russian Federation, Spain, Taiwan, United Kingdom, and United States of America. NATALEE enrolled 83 patients from 11 centres across the United Kingdom.
Trial design	Phase III, multi-centre, randomised, open-label trial of ribociclib plus AI vs AI, in patients with HR+/HER2– EBC at high risk of recurrence.
Duration of study	The study consisted of a 28-day Screening phase, a 60-month Treatment phase (including a 30-day Safety follow-up), and Follow-up phase (including efficacy and survival assessment).
Method of randomisation	Patients were randomly assigned to the investigational arm (ribociclib plus AI) or control arm (AI) in a 1:1 ratio through an IRT, and using the following stratification factors: • Menopausal status: premenopausal women and men vs postmenopausal women • AJCC 8th edition Anatomic Stage Group: Anatomic Stage Group II vs Anatomic Stage Group III (enrolment of patients with Anatomic Stage Group II was limited to 40%) • Prior neoadjuvant/adjuvant chemotherapy: yes vs no • Geographical region: North America/Western Europe/Oceania vs ROW
Method of blinding	This was an open-label study as the AEs associated with the study treatments were not likely to be compatible with maintaining a blinded study. However, to minimise bias during data review, the study team was blinded to aggregate reports by treatment arm until the time of the final iDFS analysis (or until after interim iDFS analysis if futility or superiority was declared).
Trial drugs and method of administration	• **Ribociclib plus AI (investigational):** Patients received the AI as outlined in the control arm below. In addition, patients received oral ribociclib 400 mg (2 x 200 mg tablets) once daily on days 1 to 21 in each 28-day cycle, followed by 7 days off ribociclib (days 22 to 28) for up to 36 months (approximately 39 cycles), or until guidelines for discontinuation of treatment were met. • **AI (control):** Patients in both arms were treated with a standard NSAI, either letrozole (2.5 mg oral tablet once daily continuously) or anastrozole (1 mg oral tablet once daily continuously) for 60 months; the choice between letrozole and anastrozole was at the investigator's discretion. Premenopausal women and men were also administered goserelin (3.6 mg) every 4 weeks subcutaneously for 60 months. Patients who permanently discontinued AIs while receiving ribociclib had to discontinue ribociclib at the same time. Patients who permanently discontinued ribociclib for any reason proceeded to the 30-day Post Ribociclib Safety Follow-up visit, and continued on AIs within the Treatment Phase of the trial.
	All concomitant medications and significant non-drug therapies (including physical therapy, vitamins, herbal/natural medications and blood transfusions) administered from 30 days before randomisation until 36 months after the randomisation date were recorded on a

<table>
<tr><td rowspan="2">Permitted and disallowed concomitant medication</td><td colspan="2">case report form. Patients taking concomitant medication chronically were maintained on the same dose and dose schedule throughout the trial period, where medically feasible and indicated.</td></tr>
<tr><td>Permitted therapies
Standard neoadjuvant and/or adjuvant ET initiated within 12 months of randomisation
Medications required to treat AEs, manage cancer symptoms, concurrent diseases and supportive care agents, such as pain medications, antiemetics and anti-diarrhoeals
Bone-modifying agents (e.g. bisphosphonates, denosumab)</td><td>Prohibited therapies
Hormonal contraception (including the use of an intrauterine system) or hormonal medications used as HRT for symptoms of menopause, phytoestrogens
Strong inhibitors or inducers of CYP3A4/5
Substrates of CYP3A4/5 with a narrow therapeutic index
Medications with a known risk for QT prolongation and/or TdP
Concomitant tamoxifen or toremifene use
Participation in other studies involving investigational drug(s) within 30 days prior to randomisation or within 5 half-lives of the investigation drug(s) (whichever is longer), or participation in any other type of medical research judged not to be scientifically or medically compatible with the NATALEE trial</td></tr>
<tr><td>Primary endpoints (including scoring methods and timings of assessments)</td><td colspan="2">The primary endpoint was iDFS, defined by the STEEP criteria[90] as the time from date of randomisation to the date of the first event of:
first event of local invasive breast recurrence
regional invasive recurrence
distant recurrence
death (any cause)
contralateral invasive breast cancer
second primary non-breast invasive cancer (excluding basal and squamous cell carcinomas of the skin)</td></tr>
<tr><td>Secondary endpoints (including scoring methods and timings of assessments)</td><td colspan="2">Secondary efficacy endpoints
RFS, defined by the STEEP criteria,[90] as the time from date of randomisation to date of first event of local invasive breast recurrence, regional invasive recurrence, distant recurrence or death (any cause)
DDFS, defined by the STEEP criteria,[90] as the time from date of randomisation to date of first event of distant recurrence, death (any cause), or second primary non-breast invasive cancer (excluding basal and squamous cell carcinomas of the skin)
OS, defined as the time from date of randomisation to date of death due to any cause
Patient-reported outcomes
The PROs administered were the EORTC QLQ-C30, EORTC QLQ-BR23, EQ-5D-5L and HADs
For each PRO, patients were administered paper questionnaires at the screening visit, at visits every 12 weeks during the first 24 months and every 24 weeks thereafter until distant recurrence, at end of treatment, at confirmation of first recurrence, at confirmation of distant recurrence, and at visits during the first 12 months after confirmation of distant recurrence (every 12 weeks if</td></tr>
</table>

	confirmation happened during first 24 months after randomisations, or every 24 weeks if confirmation happened after first 24 months after randomisation) • Collection of all PRO measures had a ±3-week window, unless otherwise indicated • All paper questionnaires were in the patient's local language and were administered at the beginning of the visit, prior to any interaction with the investigator **Safety** • All AEs (including laboratory abnormalities) were reported and graded using the NCI CTCAE v4.03. AE duration, relationship to the trial treatment, action taken with respect to trial treatment, any other action taken, AE severity, and the outcome of the AE were also evaluated. AEs were followed until resolution, until judged to be permanent, the patient was lost to follow-up, or the patient withdrew consent. • All SAEs, defined as any AE meeting at least one of the following conditions: ○ is fatal ○ is life-threatening (i.e., the AE, in the view of the Investigator, places the patient at immediate risk of death at the time of occurrence) ○ requires inpatient hospitalisation or prolongation of existing hospitalisation ○ results in persistent or significant disability/incapacity ○ constitutes a congenital anomaly/birth defect ○ is medically significant, i.e., defined as an event that jeopardises the patient or may require medical or surgical intervention to prevent one of the outcomes listed above • Physical examinations • Performance status, assessed according to the ECOG Performance Status Scale • ECG • Height, weight and vital signs (body temperature, pulse rate, blood pressure) measured at regular intervals • Laboratory evaluations (haematology, biochemistry, coagulation, and other required tests) **Pharmacokinetics** • Pharmacokinetic samples were analysed using liquid chromatography-tandem mass spectrometry with a lower limit of quantification of 1.00 ng/mL
Pre-specified subgroup analyses	Subgroup analyses of iDFS were performed for each of the following subgroups: • Stratification factors • Gender (women vs men) • Prior radiation therapy (Yes vs No) • Prior mastectomy (Yes vs No) • Race (Asian vs non-Asian) • Region (Europe, North America/Australia, Asia, Latin America) • Age category 1 (<45 vs 45-54 vs 55-64 vs ≥65)

	• Age category 2 (< median vs ≥ median) • Type of ET (letrozole vs anastrozole) • ER+/PR+ vs ER–/PR+ vs ER+/PR– • Number of positive lymph nodes at study entry: 0 lymph nodes vs 1-3 lymph nodes vs ≥4 lymph nodes • Tumour stage at time of surgery: T1–2 vs T3–T4 • Histological grade at time of surgery: grade 1 vs grade 2 vs grade 3, • Ki67 status from archival tumour analysed by central laboratory: ≤20% vs >20% • BMI ≥25 vs <25

Abbreviations: AE: adverse event; AI: aromatase inhibitors; AJCC: American Joint Committee on Cancer; BC: breast cancer; BMI: body mass index; CYP3A4/5: cytochrome P450 3A4/5; DDFS: distant disease-free survival; EBC: early breast cancer; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-BR23: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Specific; EQ-5D-5L: EuroQol five-dimensional five-level questionnaire; ER: oestrogen receptor; ET: endocrine therapy; HADs: Hospital Anxiety and Depression Scale; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; HRT: hormone replacement therapy; iDFS: invasive disease-free survival; IRT: interactive response technology; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; NSAI: non-steroidal aromatase inhibitor; OS: overall survival; PK: pharmacokinetics; PR: progesterone receptor; PRO: patient reported outcome; RFS: recurrence-free survival; ROW: rest of world; SAE: serious adverse event; STEEP: Standardised Definitions for Efficacy End Points; TdP: torsades de pointes.
Sources: Novartis Data on File: NATALEE Protocol.[2]

Data cut-offs

In total, five data cuts from the NATALEE trial are available at the time of this submission:

- Interim analysis 1 (IA1) (data cut-off: 3rd September 2021) was planned after approximately 40% iDFS events (approximately 200 events) and was conducted to allow the trial to stop for futility
- IA2 (data cut-off: 15th August 2022) was planned to be performed at approximately 70% iDFS events (approximately 350 iDFS events)
- IA3 (data cut-off: 11th January 2023) was planned to be performed at approximately 85% iDFS events (approximately 425 iDFS events) to allow the trial to declare outstanding efficacy. The median follow-up time was 34.0 months; the median iDFS follow-up time was 27.7 months
- The primary pre-planned analysis of iDFS (PA) (data cut-off: 21st July 2023) was planned after 500 iDFS events occurred. The median follow-up time was [redacted] months; the median iDFS follow-up time was 33.3 months
- The latest data cut available is from April 2024. At the April 2024 data cut (data cut-off: 29th April 2024), the median follow-up time was [redacted] months; the median iDFS follow-up time was 44.2 months.

Later data cuts from the NATALEE trial are planned for the second half of 2025, 2026 and 2027, and therefore it is not anticipated that additional data (beyond the April 2024 data cut) will become available during this appraisal.

This submission presents data from the IA3 (January 2023), PA (July 2023) and the April 2024 data cuts of NATALEE (Table 7). In the following sections, results are presented for the primary and secondary outcomes from the PA (July 2023) and the April 2024 data cut. Results for exploratory outcomes were not available at PA nor the April 2024 data cut and therefore these are presented from IA3 (January 2023). Safety data presented in the following sections are from the April 2024 data cut. For completeness, further results from IA3 (January 2023) and PA (July 2023) are presented in Appendix N and Appendix O, respectively.

Table 7: Summary of presented data from NATALEE

Data cut	Primary efficacy outcome	Secondary efficacy outcomes	Exploratory outcomes	Patient-reported outcomes	Safety outcomes
April 2024 data cut	✓ (Section B.2.5.1)	✓ (Section B.2.5.2)	✓ (Appendix P)	N/A	✓ (Section B.2.9)
PA (July 2023)	✓ (Section B.2.5.1)	✓ (Section B.2.5.2)	N/A	N/A	✓ (Appendix O)
IA3 (January 2023)	✓ (Appendix N)	✓ (Appendix N)	N/A	✓ (Section B.2.5.4; Appendix N)	✓ (Appendix N)

Abbreviations: IA3: interim analysis 3; N/A: not applicable; PA: primary pre-planned analysis of iDFS.

Eligibility criteria

An overview of the key eligibility criteria for the NATALEE trial are presented in Table 8. Full inclusion and exclusion criteria are presented in the NATALEE protocol.[2]

Table 8: NATALEE key inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria
• Male or female ≥18 years-old at the time of consent with known menopausal status • Histologically confirmed unilateral primary invasive adenocarcinoma of breast within 18 months prior to randomisation, or multicentric and/or multifocal tumour if all histopathologically examined lesions meet pathologic inclusion criteria • Confirmed HR+ (ER+ and/or PR+), HER2– BC • Anatomic Stage Group III, Anatomic Stage Group IIB or Anatomic Stage Group IIA that is N1, or N0 (Grade 3, or Grade 2 meeting specific criteria) • If indicated, had completed adjuvant and/or neoadjuvant chemotherapy • If indicated, had completed adjuvant and/or neoadjuvant radiotherapy • No contraindication for the adjuvant ET used in NATALEE, and intended to be treated with ET for 5 years or more • Post-surgical resection where tumour was removed completely • Previous standard neoadjuvant and/or adjuvant ET initiated within 12 months of trial randomisation • ECOG Performance Status of 0 or 1 • Adequate bone marrow and organ function • Standard 12-lead ECG values	• Previously received any CDK4/6 inhibitor • Prior treatment with tamoxifen, raloxifene or AIs for reduction in risk of breast cancer and/or treatment for osteoporosis within the last 2 years prior to randomisation. Concurrently using HRT. Concurrently using other antineoplastic therapy with the exception of adjuvant ET. • Prior treatment with anthracyclines at cumulative doses of 450 mg/m^2 or more for doxorubicin, or 900 mg/m^2 or more for epirubicin • Known hypersensitivity to any excipients of ribociclib and/or ET • Distant metastases of breast cancer beyond regional lymph nodes, and/or evidence of recurrence after curative surgery • Major surgery, chemotherapy, or radiotherapy within 14 days prior to randomisation • Current invasive malignancy or priori invasive malignancy whose treatment was completed within 2 years before randomisation • Clinically significant, uncontrolled heart disease and/or cardiac repolarisation abnormality • Receiving strong CYP3A4/5 inhibitors or inducers, or medications with a narrow therapeutic window, predominantly metabolised through CYP3A4/5 • Pregnant or breast-feeding (lactating) women or women who planned to become pregnant or breast-feed during the trial

Abbreviations: AI: aromatase inhibitor; CDK: cyclin dependent kinases; CYP: cytochrome; ECOG: Eastern Cooperative Oncology Group; ECG: electrocardiogram; ER: oestrogen receptor; ET: endocrine therapy; HER2: human epidermal growth factor receptor; HR: hormone receptors; HRT: hormone replacement therapy; PR: progesterone receptor.
Source: Novartis Data on File: NATALEE Protocol.[2]

B.2.3.2 Baseline characteristics

Baseline demographic characteristics for patients included in the NATALEE trial (Population 1 [NATALEE ITT]) are presented in Table 9. Baseline demographic characteristics were well-balanced across the two arms. Both trial arms consisted of 99.6% women and 0.4% men, and the median age of patients at baseline was 52.0 years. The majority of patients had an ECOG performance status of 0 (82.6% in the ribociclib plus AI arm, 83.5% in the AI arm).

Both trial arms were also well balanced with respect to baseline disease characteristics

(including Anatomic Stage Group and nodal status) as shown in Table 10. The majority of patients (3,739 [73.3%]) presented with invasive ductal carcinoma, and a total of 378 patients (14.8%) in the ribociclib plus AI arm and 418 patients (16.4%) in the AI arm were N0 on surgical specimen. The proportion of patients with Anatomic Stage Group II disease was also well balanced between both treatment arms: 39.7% of patients in the ribociclib plus AI arm and 40.5% of patients in the AI arm. Similarly for Anatomic Stage Group III disease, a balance between both treatment arms was observed (59.9% of patients in the ribociclib plus AI arm vs 59.2% of patients in the AI arm).

Table 11 presents the antineoplastic therapy received by patients prior to entry into NATALEE. Overall, [redacted] and [redacted] of patients had received any type of previous cancer therapy in the neo-adjuvant and adjuvant settings, respectively. The two trial arms were well balanced with respect to previous cancer therapy, including prior adjuvant chemotherapy (48.0% vs 47.8%), neo-adjuvant chemotherapy (42.6% vs 42.9%), ET (71.6% vs 70.6%), antineoplastic radiotherapy ([redacted]), and surgery ([redacted]). [redacted] were the most common prior chemotherapy in both trial arms (received by [redacted] of patients in the ribociclib plus AI arm and [redacted] of patients in the AI arm); GnRH analogues were received by a quarter (25.3%) of the total trial population.

Per protocol, patients were allowed to initiate adjuvant ET up to 12 months before enrolling in the trial. A total of 1,824 patients (71.6%) in the ribociclib plus AI arm and 1,801 patients (70.6%) in the AI arm had received prior ET. AIs were the most common prior ET in both treatment arms (received by 62.8% of patients in the ribociclib plus AI arm and 62.4% of patients in the AI arm). The median duration of prior ET was [redacted] months (min to max: [redacted]) in the ribociclib plus AI arm and [redacted] months (range: [redacted]) in the AI arm.

Overall, patients in NATALEE are considered representative of the population of patients with HR+/HER2– EBC at high risk of recurrence in UK clinical practice. Slight differences discussed at an advisory board meeting with six clinical experts in attendance related to the low proportion of node-negative patients (28.1% at diagnosis; 15.6% on surgical specimen), and the high proportion of patients treated with prior chemotherapy (88.1%) compared with what might be expected in UK clinical practice. Clinical experts highlighted that healthcare professionals would be more likely to enrol node-positive patients into NATALEE due to the increased risk of recurrence among these patients. It was also noted that patient enrolment into NATALEE was prior to publication of RxPONDER results, which demonstrated the lower benefit of treatment with chemotherapy in post-menopausal women (see Appendix Q.2).

Table 9: Baseline demographic characteristics in NATALEE – FAS (Population 1 [NATALEE ITT])

Characteristic	Ribociclib plus AI (N=2,549) n (%)	AI (N=2,552) n (%)	Total (N=5,101) n (%)
Sex			
Female, n (%)	2,538 (99.6)	2,543 (99.6)	5,081 (99.6)
Male, n (%)	11 (0.4)	9 (0.4)	20 (0.4)
Age group			
<45	[redacted]	[redacted]	[redacted]
45 to 54	[redacted]	[redacted]	[redacted]
55 to 64	[redacted]	[redacted]	[redacted]
≥65	[redacted]	[redacted]	[redacted]
Age, years			
n	2,549	2,552	5,101
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	52.0 (24, 90)	52.0 (24, 89)	52.0 (24, 90)
Menopausal status			
Pre-menopausal women and men	1,125 (44.1)	1,128 (44.2)	2,253 (44.2)
Post-menopausal women	1,424 (55.9)	1,424 (55.8)	2,848 (55.8)
Race			
White	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Native Hawaiian or Other Pacific Islander	[redacted]	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Ethnicity			

Hispanic or Latino	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Region			
Asia	281 (11.0)	290 (11.4)	571 (11.2)
Europe	1,505 (59.0)	1,506 (59.0)	3,011 (59.0)
North America/Australia	624 (24.5)	612 (24.0)	1,236 (24.2)
Latin America	139 (5.5)	144 (5.6)	283 (5.5)
ECOG performance status			
0	2,106 (82.6)	2,132 (83.5)	4,238 (83.1)
1	440 (17.3)	418 (16.4)	858 (16.8)
Missing	3 (0.1)	2 (0.1)	5 (0.1)
Weight (kg)			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
Height (cm)			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
BMI			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]

Footnotes: Weight and height are the last non-missing assessments on or before the date of randomisation. BMI is calculated based on raw data measurements.
Abbreviations: BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; FAS: full analysis set; Kg: kilogram; SD: standard deviation.
Source: Novartis Data on File (NATALEE Clinical Study Report IA3: Table 10–7).[28]

Table 10: Disease characteristics in NATALEE– FAS (Population 1 [NATALEE ITT])

Disease characteristics	Ribociclib plus AI N=2,549 n (%)	AI N=2,552 n (%)	Total N=5,101 n (%)
Tumour location			
Right	[redacted]	[redacted]	[redacted]
Left	[redacted]	[redacted]	[redacted]
Bilateral	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Histopathological grade at diagnosis			
GX	30 (1.2)	32 (1.3)	62 (1.2)
G1	218 (8.6)	240 (9.4)	458 (9.0)
G2	1,458 (57.2)	1,451 (56.9)	2,909 (57.0)
G3	521 (20.4)	549 (21.5)	1,070 (21.0)
Not Done	292 (11.5)	258 (10.1)	550 (10.8)
Missing	30 (1.2)	22 (0.9)	52 (1.0)
T stage at diagnosis			
TX	[redacted]	[redacted]	[redacted]
T0	[redacted]	[redacted]	[redacted]
Tis	[redacted]	[redacted]	[redacted]
T1	[redacted]	[redacted]	[redacted]
T2	[redacted]	[redacted]	[redacted]
T3	[redacted]	[redacted]	[redacted]
T4	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
N stage at diagnosis			
NX	272 (10.7)	264 (10.3)	536 (10.5)

N0	694 (27.2)	737 (28.9)	1,431 (28.1)
N1	1,050 (41.2)	1,049 (41.1)	2,099 (41.1)
N2	332 (13.0)	292 (11.4)	624 (12.2)
N3	151 (5.9)	175 (6.9)	326 (6.4)
Missing	50 (2.0)	35 (1.4)	85 (1.7)
Ki67 score at initial diagnosis			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (Min, Max)	[redacted]	[redacted]	[redacted]
Ki67 category at initial diagnosis			
≤14%	[redacted]	[redacted]	[redacted]
>14%	[redacted]	[redacted]	[redacted]
≤20%	[redacted]	[redacted]	[redacted]
>20%	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Histopathological grade on surgical specimen			
GX	[redacted]	[redacted]	[redacted]
G1	[redacted]	[redacted]	[redacted]
G2	[redacted]	[redacted]	[redacted]
G3	[redacted]	[redacted]	[redacted]
Not Done	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
T stage on surgical specimen			
TX	[redacted]	[redacted]	[redacted]
T0	[redacted]	[redacted]	[redacted]
Tis	[redacted]	[redacted]	[redacted]
T1	[redacted]	[redacted]	[redacted]

T2	[redacted]	[redacted]	[redacted]
T3	[redacted]	[redacted]	[redacted]
T4	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
N stage on surgical specimen			
NX	2 (0.1)	5 (0.2)	7 (0.1)
N0	378 (14.8)	418 (16.4)	796 (15.6)
N1	1,062 (41.7)	1,039 (40.7)	2,101 (41.2)
N2	733 (28.8)	690 (27.0)	1,423 (27.9)
N3	372 (14.6)	399 (15.6)	771 (15.1)
Missing	2 (0.1)	1 (0.0)	3 (0.1)
Ki67 score on surgical specimen			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (Min, Max)	[redacted]	[redacted]	[redacted]
Ki67 category on surgical specimen			
≤14%	[redacted]	[redacted]	[redacted]
>14%	[redacted]	[redacted]	[redacted]
≤20%	[redacted]	[redacted]	[redacted]
>20%	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Time since initial diagnosis (months)			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (Min, Max)	[redacted]	[redacted]	[redacted]
Predominant histology			
Invasive ductal carcinoma NOS	1,857 (72.9)	1,881 (73.7)	3,738 (73.3)

Invasive lobular	455 (17.9)	450 (17.6)	905 (17.7)
Carcinoma medullary	1 (0.0)	1 (0.0)	2 (0.0)
Mucinous	17 (0.7)	16 (0.6)	33 (0.6)
Papillary	18 (0.7)	12 (0.5)	30 (0.6)
Tubular	5 (0.2)	3 (0.1)	8 (0.2)
Ductal Carcinoma In Situ	1 (0.0)	0	1 (0.0)
Lobular Carcinoma In Situ	0	0	0
Other	194 (7.6)	189 (7.4)	383 (7.5)
Missing	1 (0.0)	0	1 (0.0)
Prior surgery			
Mastectomy	[redacted]	[redacted]	[redacted]
Breast conserving surgery	[redacted]	[redacted]	[redacted]
Axillary lymph node dissection	[redacted]	[redacted]	[redacted]
Sentinel lymph node biopsy	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
HER2 ISH result prior to surgery (reported only if performed)			
Amplification	[redacted]	[redacted]	[redacted]
Non-amplification	[redacted]	[redacted]	[redacted]
Equivocal	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
HER2 ISH result from the surgical specimen (reported only if performed)			
Amplification	[redacted]	[redacted]	[redacted]
Non-Amplification	[redacted]	[redacted]	[redacted]
Equivocal	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
HER2 IHC score prior to surgery (reported only if performed)			

0	[redacted]	[redacted]	[redacted]
1+	[redacted]	[redacted]	[redacted]
2+	[redacted]	[redacted]	[redacted]
3+	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
HER2 IHC score from the surgical specimen (reported only if performed)			
0	[redacted]	[redacted]	[redacted]
1+	[redacted]	[redacted]	[redacted]
2+	[redacted]	[redacted]	[redacted]
3+	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
ER/PR combination statuses			
ER+/PR+	[redacted]	[redacted]	[redacted]
ER+/PR–	[redacted]	[redacted]	[redacted]
ER–/PR+	[redacted]	[redacted]	[redacted]
ER+/UNK	[redacted]	[redacted]	[redacted]
UNK/PR+	[redacted]	[redacted]	[redacted]
UNK/PR–	[redacted]	[redacted]	[redacted]
UNK/UNK	[redacted]	[redacted]	[redacted]
AJCC 8th edition Anatomic Stage			
Stage 0	[redacted]	[redacted]	[redacted]
Stage I	[redacted]	[redacted]	[redacted]
Stage II	[redacted]	[redacted]	[redacted]
Stage III	[redacted]	[redacted]	[redacted]
Stage IV	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Genomic test			

Endopredict	[redacted]	[redacted]	[redacted]
Mammaprint	[redacted]	[redacted]	[redacted]
Ovotype DX	[redacted]	[redacted]	[redacted]
Pam50	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
N status for subgroup analysis used in AJCC Stage derivation[1]			
N0	285 (11.2)	328 (12.9)	613 (12.0)
N1–N3	2,261 (88.7)	2,219 (87.0)	4,480 (87.8)
>N3	0	0	0
Missing	3 (0.1)	5 (0.2)	8 (0.2)

Footnotes: Subjects may have had more than one prior surgery but are only counted once per category.
T stage category T1 collects T1mi, T1a, T1b, and T1c. Category T4 collects T4a, T4b, T4c, and T4d.
N stage category N0 collects N0 and N0(i+). Category N1 collects N1, N1a, N1c, and N1mi. Category N2 collects N2a, N2b, and N2c. Category N3 collects N3a, N3b, and N3c. AJCC 8th ed. category Stage 1 collects Stage IA and Stage IB. Category Stage II collects Stage IIIA and Stage IIB. Category Stage III collects Stage IIIA, Stage IIIB, and Stage IIIC. Stage is derived using TNM from surgery for patients having not received neo-/adjuvant treatment, or as worst stage derived using TNM at diagnosis and TNM from surgery for patients having received neo-/adjuvant treatment.
Patients may have had more than one Genomic test type but are only counted once per type.
[1]Included in missing category are patients having Nx. These patients are either unable to be staged or have been staged with Nx and T4(x) as Stage IIIB.
Abbreviations: AI: aromatase inhibitor; AJCC: American Joint Committee on Cancer; ER: oestrogen receptor; ET: endocrine therapy; FAS: full analysis set; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; ISH: in situ hybridisation; M: metastases; N: node; NOS: not otherwise specified; PR: progesterone receptor; SD: standard deviation; T: tumour; UNK: unknown.
Source: Novartis Data on File (NATALEE Clinical Study Report IA3: Table 10–8).[28]

Table 11: Prior cancer therapy in NATALEE – FAS (Population 1 [NATALEE ITT])

Therapy	Ribociclib plus AI N=2,549 n (%)	AI N=2,552 n (%)	Total N=5,101 n (%)
Number of patients who received any prior anti-neoplastic medications	[redacted]	[redacted]	[redacted]
Chemotherapy	2,249 (88.2)	2,245 (88.0)	4,494 (88.1)
Anthracyclines	[redacted]	[redacted]	[redacted]
Taxanes	[redacted]	[redacted]	[redacted]

Other	[redacted]	[redacted]	[redacted]
Endocrine therapy	1,824 (71.6)	1,801 (70.6)	3,625 (71.1)
Aromatase inhibitors	1,601 (62.8)	1,592 (62.4)	3,193 (62.6)
Anti-oestrogens	344 (13.5)	341 (13.4)	685 (13.4)
Gonadotropin-releasing hormone analogues	670 (26.3)	620 (24.3)	1,290 (25.3)
Other	[redacted]	[redacted]	[redacted]
Biologic/targeted therapy	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Therapy setting			
Adjuvant	[redacted]	[redacted]	[redacted]
Adjuvant chemotherapy	1,223 (48.0)	1,220 (47.8)	2,443 (47.9)
Neo-adjuvant	[redacted]	[redacted]	[redacted]
Neo-adjuvant chemotherapy	1,085 (42.6)	1,095 (42.9)	2,180 (42.7)
Lowest ATC class			
Antineoplastic and immunomodulating agents	[redacted]	[redacted]	[redacted]
Dermatologicals	[redacted]	[redacted]	[redacted]
Musculo-skeletal system	[redacted]	[redacted]	[redacted]
Systemic hormonal preparations, excluding sex hormones and insulins	[redacted]	[redacted]	[redacted]
Various	[redacted]	[redacted]	[redacted]
Number of patients who received any prior anti-neoplastic radiotherapy	[redacted]	[redacted]	[redacted]
Time since end of last radiotherapy (months)			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
Location of last radiotherapy			

Breast	[redacted]	[redacted]	[redacted]
Chest wall	[redacted]	[redacted]	[redacted]
Axillary lymph node	[redacted]	[redacted]	[redacted]
Supraclavicular lymph node	[redacted]	[redacted]	[redacted]
Internal mammary lymph node	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Duration of prior endocrine therapy (months)			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
Number of patients who received any prior surgery	[redacted]	[redacted]	[redacted]
Time since end of last surgery (months)			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
Type of surgery			
Biopsy	[redacted]	[redacted]	[redacted]
Not Biopsy	[redacted]	[redacted]	[redacted]

Footnotes: Anti-neoplastic medications are coded using the WHO-DD Version: September 2022. Subjects may have multiple prior anti-neoplastic therapy types but are only counted once per therapy or sub-therapy type. Subjects may have multiple radiotherapy locations based on the last reported date but are only counted once per radiotherapy location. Subjects may have both adjuvant and neo-adjuvant prior therapy settings but are only counted once per therapy setting. Time since end of last radiotherapy = (randomisation date - end date of radiotherapy). Time since end of last surgery = (randomisation date - date of last surgery).
Abbreviations: AI: aromatase inhibitor; ATC: anatomical therapeutic chemical; ET: endocrine therapy; FAS: full analysis set; SD: standard deviation.
Source: Novartis Data on File (NATALEE Clinical Study Report IA3: Table 10–10).[28]

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

The study populations used for the analysis of the NATALEE trial are summarised in Table 12. All efficacy endpoints presented in this submission are based on the full analysis set (FAS) at the relevant data cut, which included all randomised participants. Safety outcomes are presented for the safety analysis set, which included all patients who received any trial treatment.

Table 12: Summary of data sets analysed in NATALEE

Study population	Description	Ribociclib plus AI (n)	AI (n)
FAS	Comprises all patients to whom trial treatment was assigned by randomisation. According to the intent-to-treat principle, patients were analysed according to the treatment arm they were randomised to and strata they were assigned to during the randomisation procedure.	2,549	2,552
Safety analysis set	Includes all randomised patients who received any trial treatment (i.e., at least one dose of ribociclib or AI. Patients were analysed according to the trial treatment actually received. The actual treatment received corresponds to: ▪ Ribociclib plus AI if patients took at least one dose of ribociclib ▪ AI if ribociclib was never received	2,526	2,441
PPS	Consists of a subset of the patients in the FAS who were compliant with requirements of the protocol. All protocol deviations or conditions leading to exclusion from the PPS are detailed in specific trial document(s)	2,496	2,422

Abbreviations: AI: aromatase inhibitor; FAS: full analysis set; PPS: per-protocol set.
Source: Novartis Data on File: NATALEE Protocol;[2] Novartis Data on File (NATALEE Clinical Study Report April 2024 Data Cut: Table 1-2).[79]

Details of the statistical methods used in the analysis of the NATALEE trial are presented Table 13.

Table 13: Statistical methods used in the analysis of NATALEE

Hypothesis objective	The primary efficacy analysis was performed by testing the null hypothesis that there would be no difference in iDFS between the treatment arm and control arm.
Statistical analysis	**Primary endpoint: iDFS** For the primary endpoint of iDFS, the analysis was based on the FAS population according to the treatment arm and strata assigned at randomisation. The Kaplan-Meier method was used to estimate the iDFS distribution for each treatment arm. The HR, along with the 95% CI, were calculated using a stratified Cox model (using the strata assigned at randomisation). **Secondary endpoints** All secondary efficacy objectives (RFS, DDFS, and OS) were analysed at the primary analysis for iDFS, and at the end of trial. Each secondary efficacy endpoint was analysed in the FAS population, according to the randomised treatment arm and strata assigned at randomisation. The secondary efficacy objectives were analysed similarly to iDFS; the distribution of each efficacy objective was estimated using the Kaplan-Meier method, and HRs and accompanying 95% CIs were calculated using a stratified Cox model based on strata assigned at randomisation. Secondary endpoints were not adjusted for multiple comparisons. OS was additionally analysed approximately two years after the primary iDFS. A 5-year OS rate of 87% in the control arm, a HR of 0.85 between the two arms, and approximately 10% of patients lost to follow-up for OS at the time of the final iDFS analysis were assumed.
Sample size, power calculation	It was planned to randomise approximately 5,000 patients in NATALEE in order to observe the targeted 500 iDFS events around 44 months after the randomisation date of the first patients. The sample size calculations were made using the software package East 6.4, and based on the following assumptions: • The 5-year iDFS rates for patients with Anatomic Stage II and Anatomic Stage III patients were assumed to be approximately 79% and 72%, respectively, based on published data • Treatment with ribociclib in addition to AI could reduce the HR for iDFS by 27%, i.e., an expected HR of 0.73 (ribociclib plus AI vs AI) • Calculation assumes analysis by a one-sided log-rank test at the overall 2.5% level of significance, patients randomised to the two treatment arms in a 1:1 ratio, and a 4-look group sequential design (with a Lan-DeMets [O'Brien-Fleming] alpha spending function and a Lan-DeMets [O'Brien-Fleming] beta spending function • An assumed enrolment rate of approximately 170 patients per month, and a 15% dropout rate by the time of the final iDFS analysis (i.e., dropout HR: 0.00629 per month)
Data management, patient withdrawals	• Missing items data in a scale were handled based on each instrument manual; no imputation was applied if the total or subscale scores were missing at a visit.

	• For the repeated measures analysis, patients with baseline and at least one non-missing postbaseline assessments were included. All available data were used in the repeated measures models for longitudinal data which assumed that the missing scores at any time point were missing-at-random. Additional sensitivity analysis was performed to assess the possible violation of missing-at-random assumption for the missing data mechanism if deemed appropriate. Details are specified in the SAP. • For iDFS, patients were censored if no iDFS event was observed prior to the analysis cut-off date. The censoring date was the date of last recurrence assessment on or prior to data cut-off • For RFS and DDFS, patients who did not have an event were censored at the last recurrence assessment on or prior to the data cut-off • For OS, if a patient was not known to have died, then OS was censored at the latest date the patient was known to be alive (on or prior to the data cut-off)

Abbreviations: AI: aromatase inhibitor; CI: confidence interval; DDFS: distant disease-free survival; FAS: full analysis set; HR: hazard ratio; iDFS: invasive disease-free survival; OS: overall survival; RFS: recurrence free-survival; SAP: statistical analysis plan.
Source: Novartis Data on File: NATALEE Protocol.[2]

B.2.4.1 Critical appraisal of the relevant clinical effectiveness evidence

A summary of the quality of the NATALEE trial, using the York Centre for Reviews and Dissemination (CRD) checklist is presented in Table 14. Whilst patients and study assessors were not blind to treatment allocation because NATALEE was an open-label trial, overall, the risk of bias in the NATALEE trial is considered to be low.

The results of the quality assessments for all other studies identified in the clinical SLR are presented in Appendix D.

Table 14: Quality assessment of the NATALEE trial

York CRD checklist	Assessment	Summary of risk of bias
Was the randomisation carried out appropriately?	Yes. All eligible patients were randomised via stratification randomisation.	Low
Was the concealment of treatment allocation adequate?	No method of concealment was not reported	Unclear
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. The treatment groups were well balanced at baseline.	Low
Were the care providers, participants and outcome assessors blind to treatment allocation?	No. This was an open-label study	High
Were there any unexpected imbalances in drop-outs between groups?	No. There were no unexpected imbalances in drop-outs between groups. The reasons for withdrawals were clearly reported and comparable across the treatment groups.	Low
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. Authors measured all the pre-specified outcomes and no evidence of measurement of more outcomes was observed	Low
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. ITT analysis was used for efficacy outcomes and mITT analysis was used for safety outcomes.	Low

Abbreviations: CRD: Centre for Reviews; ITT: intention to treat; mITT: modified intention to treat.
Source: Novartis Data on File (NATALEE Clinical Study Report IA3).[28]

B.2.5 Clinical effectiveness results of the relevant studies

Summary of the clinical effectiveness evidence of ribociclib plus AI vs AI

- This submission presents data from the IA3 of NATALEE (data cut-off: 11th January 2023), the PA (data cut-off: 21st July 2023) and the latest available data cut from April 2024 (data cut-off: 29th April 2024).

Primary endpoint (iDFS)

- At the April 2024 data cut (median follow-up: [redacted]), a total of 263/2,549 patients (10.3%) in the ribociclib plus AI arm had experienced an iDFS event compared with 340/2,552 patients (13.3%) in the AI arm. Ribociclib plus AI statistically significantly reduced the risk of developing invasive disease by 28.5% (HR: 0.715; 95% CI: 0.609, 0.840; one-sided stratified log-rank test p-value<0.0001) compared with AI, with 4-year iDFS rates of 88.5% (95% CI: [redacted]) vs 83.6% (95% CI: [redacted] in the ribociclib plus AI and AI arms, respectively.
- Subgroup analyses of iDFS demonstrated a consistent treatment effect across key stratification factors and subgroups. Specifically, at the April 2024 data cut, the iDFS HR for ribociclib plus AI vs AI was 0.731 (95% CI: 0.617, 0.866) in Population 2 (NATALEE node-positive high-risk), representing a 26.9% relative reduction in risk of an iDFS event, and 0.666 (95% CI: 0.397, 1.118) in Population 3 (NATALEE node-negative high-risk), representing a 33.4% relative reduction in risk of an iDFS event,

Secondary endpoints (RFS, DDFS and OS)

- At the April 2024 data cut, RFS results showed that ribociclib plus AI resulted in a statistically significant [redacted] relative reduction in the risk of a patient experiencing disease recurrence [redacted], while DDFS results showed a statistically significant 28.5% relative reduction in the risk of a distant recurrence among patients in the ribociclib plus AI arm (HR: 0.715; 95% CI: 0.604, 0.847, one-sided stratified log-rank test p-value<0.0001) compared with patients in the AI arm.
- At the April 2024 data cut, an OS trend in favour of ribociclib plus AI vs AI was observed (HR: 0.827; 95% CI: 0.636, 1.074, one-sided stratified log-rank test p-value=0.0766), supporting the strength of the evidence that there is no deterioration in OS following treatment with ribociclib plus AI.

Patient-reported outcomes

- At IA3, EORTC QLQ-C30 physical functioning scores [redacted] between treatment arms, with [redacted] observed at any post-baseline timepoint through to end of treatment, demonstrating that ribociclib to AI did not compromise patient HRQoL.

NATALEE data presentation

Where available, data from the PA (data cut-off: 21st July 2023; median follow-up: [redacted] months; median iDFS follow-up: 33.3 months) and the April 2024 data cut (data cut-off: 29th April 2024; median follow-up: [redacted]; median iDFS follow-up: 44.2 months) are presented in the following sections.

Where data for certain outcomes are not available, data from IA3 (data cut-off: 11th January 2023; median follow-up: 34.0 months; median iDFS follow-up: 27.7 months) are presented instead (see Table 7 for a summary of the presented data from NATALEE in this submission). For completeness, further efficacy data from IA3 (January 2023) are presented in Appendix N.

B.2.5.1 Primary endpoint

Invasive disease-free survival (iDFS)

At the PA (July 2023) of the NATALEE trial for Population 1 (NATALEE ITT), ribociclib plus AI statistically significantly reduced the relative risk of an iDFS event compared with AI by 25.1%. At the April 2024 data cut, the reduction in the relative risk of an iDFS event with ribociclib plus AI vs AI increased from the previous data cut to 28.5%

A summary of iDFS results in the FAS population (Population 1 [NATALEE ITT]) at the PA (July 2023) and the April 2024 data cut are presented in Table 15 and Table 16, respectively.

iDFS is considered a clinically meaningful surrogate endpoint for OS, as disease recurrence is associated with breast cancer mortality. In addition to the increased mortality risk, prevention of disease recurrence also avoids the reduced HRQoL and increased symptom burden of advanced or metastatic disease (see Section B.1.3.5). The composite measure of iDFS incorporates a broad range of invasive local, regional, and distant recurrences, contralateral breast, types of new cancer events or death from any cause, and therefore the statistically significant and clinically meaningful improvement in the risk of experiencing an iDFS event observed in NATALEE is a key indicator of the efficacy of ribociclib in this patient population.

At both the PA (July 2023) and the April 2024 data cut (performed at 509 and 603 iDFS events, respectively) in Population 1 (NATALEE ITT), the iDFS results met the criteria to demonstrate statistically significant and clinically superior efficacy for ribociclib plus AI vs AI. At the PA (July 2023), a total of 226/2,549 patients (8.9%) in the ribociclib plus AI arm had an iDFS event compared with 283/2,552 patients (11.1%) in the AI arm; a stratified Cox regression model estimated an 25.1% relative reduction in the risk of an iDFS event for patients in the ribociclib plus AI arm compared with the risk of an iDFS event for patients in the AI arm (HR: 0.749; 95% CI: 0.628, 0.892; [redacted]) (Table 15).

At the April 2024 data cut (median follow-up for iDFS: 44.2 months), the number of iDFS events had increased to 263/2,549 patients (10.3%) in the ribociclib plus AI arm, and 340/2,552 (13.3%) patients in the AI arm, respectively. There was a statistically significant improvement in the risk of an iDFS event in the ribociclib plus AI arm compared with AI arm (one-sided stratified log-rank test p-value<0.0001). The relative reduction in the risk of an iDFS event for patients in the ribociclib plus AI arm compared with the risk of an iDFS event for patients in the AI arm had increased at the April 2024 data cut to 28.5% (HR: 0.715; 95% CI: 0.609, 0.840); one-sided stratified log-rank test p-value <0.0001). The 4-year iDFS rates at the April 2024 data cut were 88.5% (95% CI: [redacted]) in the ribociclib plus AI arm, and 83.6% (95% CI: [redacted]) in the AI arm, reflecting a 4.9% absolute benefit favouring ribociclib plus AI.

Figure 8 and Figure 9 present the Kaplan-Meier iDFS curves for the PA (July 2023) and the April 2024 data cut, respectively, for Population 1 (NATALEE ITT). The curves diverge from approximately 3 months after the start of treatment, which corresponds to the time of the first STEEP clinical evaluation. In general, the iDFS event-free probability remained higher in the ribociclib plus AI arm, which indicates an early sustained benefit with ribociclib plus AI. Notably,

at the April 2024 data cut, a limited number of patients were at risk at 60 months (8 patients in the ribociclib plus AI arm, and 6 patients in the AI arm) and therefore the iDFS rate beyond 60 months should be interpreted with caution (Figure 8). Likewise, the iDFS rate beyond 48 months for the PA (July 2023) data should be interpreted with caution (due to low numbers of patients at risk; Figure 9).

Table 15: Summary of iDFS in NATALEE (PA [July 2023]) – FAS (Population 1 [NATALEE ITT])

	Ribociclib plus AI (N=2,549)	AI (N=2,552)
Median follow-up in months	33.3	
Number of events, n (%)	226 (8.9)	283 (11.1)
p-value log-rank[a]	[redacted]	
HR (95% CI)	0.749 (0.628, 0.892)	
3-year iDFS rate, % (95% CI)	90.7 (89.3, 91.8)	87.6 (86.1, 88.9)

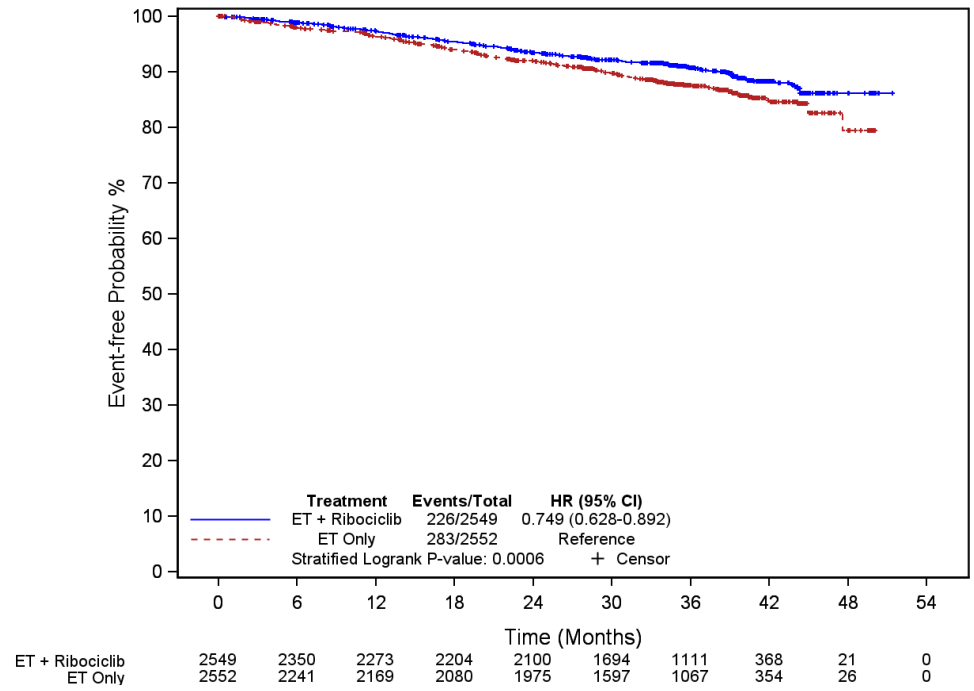
Footnotes: [a] 1-sided p-value for log-rank test stratified by premenopausal women and men vs postmenopausal women, anatomic stage group II vs anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs no) and North America/Western Europe/Oceania vs rest of world.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; FAS: full analysis set; HR: hazard ratio; iDFS: invasive disease-free survival; PA: primary pre-planned analysis of iDFS.
Source: Novartis Data on File (NATALEE Clinical Study Report Primary Pre-Planned Analysis of iDFS: Table 4.1-1).[92]

Table 16: Summary of iDFS in NATALEE (April 2024 data cut) – FAS (Population 1 [NATALEE ITT])

	Ribociclib plus AI (N=2,549)	AI (N=2,552)
Median follow-up in months	44.2	
Number of events, n (%)	263 (10.3)	340 (13.3)
p-value[a]	<0.0001	
HR (95% CI)	0.715 (0.609, 0.840)	
3-year iDFS rate, % (95% CI)	90.8 [redacted]	88.1 [redacted]
4-year iDFS rate, % (95% CI)	88.5 [redacted]	83.6 [redacted]

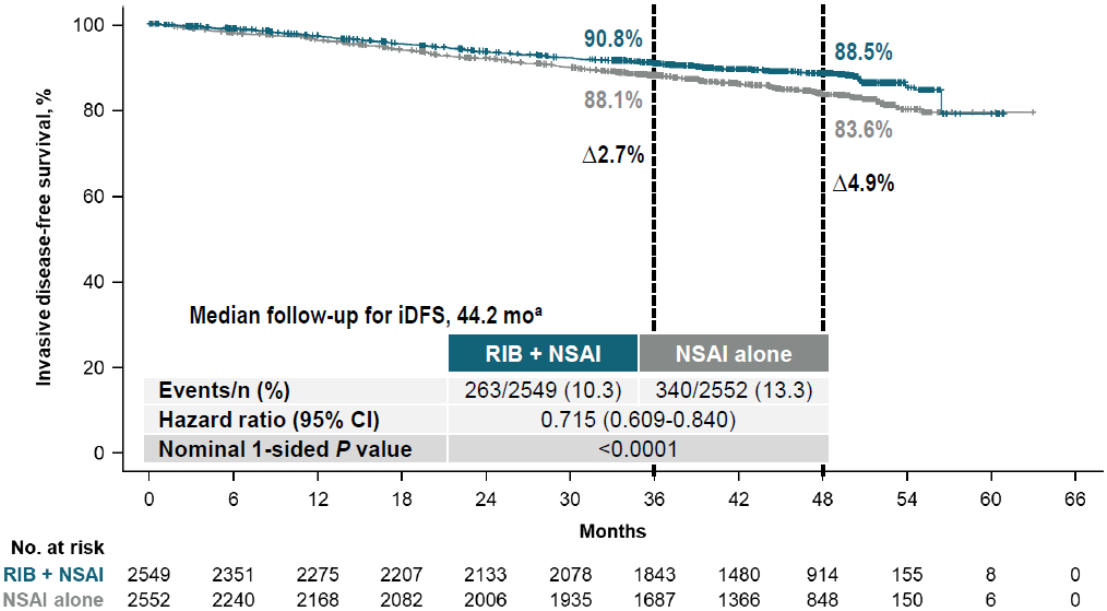
Footnotes: Hazard rate in group ribociclib plus AI vs hazard rate in group AI only is computed using the Cox proportional hazards model with treatment as a single covariate and premenopausal women and men vs postmenopausal women, anatomic stage group II vs anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs no) and North America/Western Europe/Oceania vs rest of world as stratification factors. The group AI only is the reference in the hazard ratio calculation.
[a] 1-sided p-value for log-rank test stratified by premenopausal women and men vs postmenopausal women, anatomic stage group II vs anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs no) and North America/Western Europe/Oceania vs rest of world.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; FAS: full analysis set; HR: hazard ratio; iDFS: invasive disease-free survival.
Source: Fasching *et al.* (2024);[93] Novartis Data on File (NATALEE Clinical Study Report April 2024 Data Cut: Table 2-1).[79]

Figure 8: Kaplan-Meier plot for iDFS in NATALEE (PA [July 2023]) – FAS (Population 1 [NATALEE ITT])



Footnotes: As only AI therapies were received in the NATALEE trial, the "ET" component of the intervention and comparator arm represents AI.
p-value from stratified log-rank test is one-sided.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; ET: endocrine therapy; FAS: full analysis set; HR: hazard ratio; iDFS: invasive disease-free survival; PA: primary pre-planned analysis of iDFS.
Source: Novartis Data on File (NATALEE Clinical Study Report Primary Pre-Planned Analysis of iDFS: Figure 4.1-1).[92]

Figure 9: Kaplan-Meier plot for iDFS in NATALEE (April 2024 data cut) – FAS (Population 1 [NATALEE ITT])



Footnotes: [a] An additional 10.9 months of follow-up compared with the protocol-specified final iDFS analysis.
Abbreviations: CI: confidence interval; FAS: full analysis set; iDFS: invasive disease-free survival; mo: months; NSAI: non-steroidal aromatase inhibitor; RIB: ribociclib.
Source: Fasching *et al.* (2024).[93]

B.2.5.2 Secondary endpoints

Several secondary endpoints were assessed in NATALEE. The secondary endpoints from the PA (July 2023) and the April 2024 data cut presented in this section are RFS, DDFS and OS (all assessed in the FAS i.e., Population 1 [NATALEE ITT]). Secondary endpoint data from IA3 (January 2023) are presented in Appendix N.

Recurrence-free survival

At the PA (July 2023) of the NATALEE trial in Population 1 (NATALEE ITT), ribociclib plus AI statistically significantly reduced the relative risk of disease recurrence compared with AI, by 27.3%. At the April 2024 data cut, the relative reduction in the risk of disease recurrence with ribociclib plus AI vs AI increased from the previous data cut to [redacted]. The RFS results supported the primary efficacy results

A summary of RFS in the FAS population (Population 1 [NATALEE ITT]) at the PA (July 2023) and the April 2024 data cut is shown in Table 17 and Table 18, respectively. RFS is a key efficacy endpoint in EBC, as recurrent disease may progress to advanced or metastatic disease (which has considerably worse outcomes), and patients with recurrent disease often experience reduced HRQoL compared with those without recurrent disease. RFS is therefore an important endpoint to assess when considering EBC treatment efficacy.

At the PA (July 2023) in Population 1 (NATALEE ITT) in the ribociclib plus AI arm, 192/2,549 (7.5%) patients had an RFS event compared with 248/2,552 (9.7%) patients in the AI arm; there was an estimated 27.3% relative reduction in the risk of RFS for patients in the ribociclib plus AI arm (HR: 0.727; 95% CI: 0.602, 0.877, [redacted]).

At the April 2024 data cut, the number of RFS events had increased to [redacted] and [redacted] for the ribociclib plus AI arm and AI arm, respectively. The relative reduction in the risk of disease recurrence in the ribociclib plus AI arm compared with the AI arm had increased to [redacted]

The RFS distributions at the PA (July 2023) and the April 2024 data cut, estimated using the Kaplan-Meier method (Figure 10 and Figure 11, respectively), were consistent with the primary iDFS results.

Table 17: Summary of RFS in NATALEE (PA [July 2023]) – FAS (Population 1 [NATALEE ITT])

	Ribociclib plus AI (N=2,549)	AI (N=2,552)
Number of events, n (%)	192 (7.5)	248 (9,7)
Nominal p-value (1-sided)	[redacted]	
HR (95% CI)	0.727 (0.602, 0.877)	

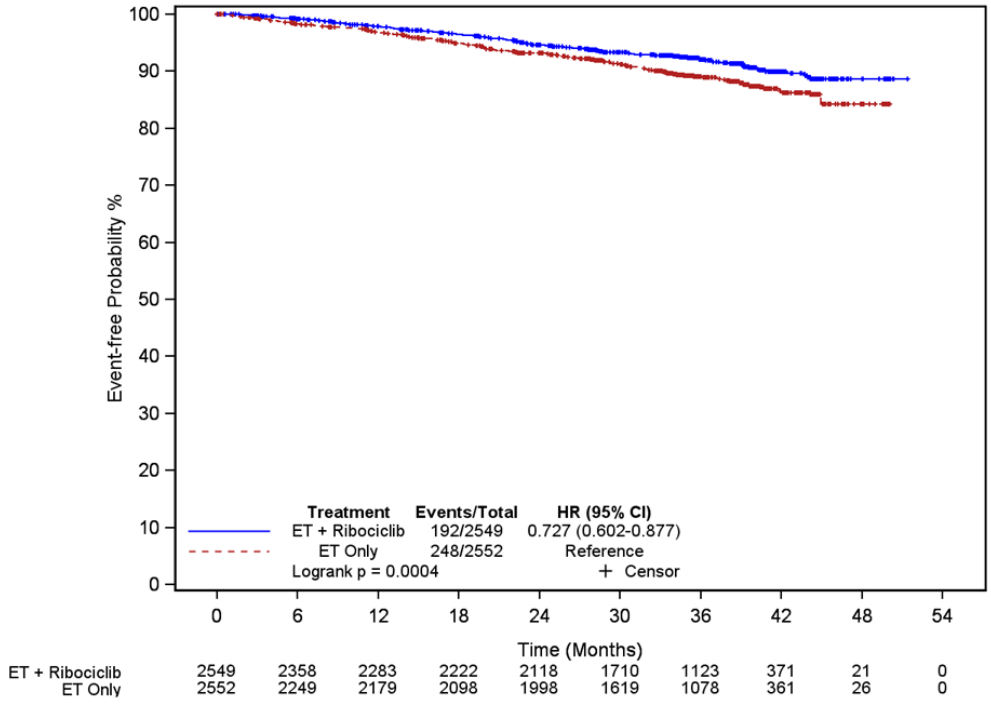
Footnotes: Censoring date is the last assessment before the earliest of the following: analysis cut-off date, date of consent withdrawal, or date of last contact.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; FAS: full analysis set; HR: hazard ratio; PA: primary pre-planned analysis of iDFS; RFS: recurrence-free survival.
Source: Novartis Data on File (NATALEE Clinical Study Report Primary Pre-Planned Analysis of iDFS).[92]

Table 18: Summary of RFS in NATALEE (April 2024 data cut) – FAS (Population 1 [NATALEE ITT])

	Ribociclib plus AI (N=2,549)	AI (N=2,552)
Number of events, n (%)	[redacted]	[redacted]
p-value (1-sided)[a]	[redacted]	
HR (95% CI)	[redacted]	
3-year RFS rate, % (95% CI)	[redacted]	[redacted]
4-year RFS rate, % (95% CI)	[redacted]	[redacted]

Footnotes: [a]1-sided p-value for log-rank test stratified by premenopausal women and men vs postmenopausal women, anatomic stage group II vs anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs no) and North America/Western Europe/Oceania vs rest of world.
Hazard rate in group ribociclib plus AI vs hazard rate in group AI is computed using the Cox proportional hazards model with treatment as a single covariate and premenopausal women and men vs postmenopausal women, anatomic stage group II vs anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs no) and North America/Western Europe/Oceania vs rest of world as stratification factors. The group AI is the reference in the hazard ratio calculation.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; FAS: full analysis set; HR: hazard ratio; RFS: recurrence-free survival.
Source: Novartis Data on File (NATALEE Clinical Study Report April 2024 Data Cut: Table 3-1).[79]

Figure 10: Kaplan-Meier plot for RFS in NATALEE (PA [July 2023]) – FAS (Population 1 [NATALEE ITT])



Footnotes As only AI therapies were received in the NATALEE trial, the "ET" component of the intervention and comparator arm represents AI.
p-value from stratified log-rank test is one-sided.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; ET: endocrine therapy; FAS: full analysis set; HR: hazard ratio; PA: primary pre-planned analysis of iDFS; RFS: recurrence-free survival.
Source: Novartis Data on File (NATALEE Clinical Study Report Primary Pre-Planned Analysis of iDFS: Figure 4.2-1).[92]

Figure 11: Kaplan-Meier plot for RFS in NATALEE (April 2024 data cut) – FAS (Population 1 [NATALEE ITT])

Footnotes: As only AI therapies were received in the NATALEE trial, the "ET" component of the intervention and comparator arm represents AI.
p-value from stratified log-rank test is one-sided.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; ET: endocrine therapy; FAS: full analysis set; HR: hazard ratio; RFS: recurrence-free survival; NE: not estimable.
Source: Novartis Data on File (NATALEE Clinical Study Report April 2024 Data Cut: Figure 3-1).[79]

Distant disease-free survival

At the PA (July 2023) of the NATALEE trial in Population 1 (NATALEE ITT), ribociclib plus AI statistically significantly reduced the relative risk of distant disease compared with AI, by 25.1%. At the April 2024 data cut, the relative reduction in the risk of distant disease with ribociclib plus AI Vs AI increased from the previous data cut-off to 28.5%

An overview of DDFS in the FAS population (Population 1 [NATALEE ITT]) at the PA (July 2023) and the April 2024 data cut is shown in Table 19 and Table 20, respectively. Distant recurrence indicates that breast cancer has progressed to advanced or metastatic disease, marking the transition from curable to incurable disease and significantly reducing the likelihood of survival. As such, improving DDFS rates is a key endpoint in the treatment of EBC.

At the PA (July 2023), in the ribociclib plus AI arm, 204/2,549 (8.0%) patients had a DDFS event compared with 256/2,552 (10.0%) patients in the AI arm; there was an estimated 25.1% relative reduction in the risk of an DDFS event for patients in the ribociclib plus AI arm (HR: 0.749; 95% CI: 0.623, 0.900, [redacted]).

At the April 2024 data cut, the number of DDFS events had increased to 240/2,549 (9.4%) and 311/2,552 (12.2%) in the ribociclib plus AI arm and AI arm, respectively. The estimated reduction in the relative risk of distant disease in the ribociclib plus AI arm compared with the AI arm had also increased to 28.5% (HR: 0.715; 95% CI: 0.604, 0.847, one-sided stratified log-rank test p-value<0.0001) as of the April 2024 data cut.

Figure 12 and Figure 13 presents the Kaplan-Meier curves for DDFS at the PA (July 2023) and

the April 2024 data cut, respectively. The DDFS distribution is consistent with the primary iDFS results.

Table 19: Summary of DDFS in NATALEE (PA [July 2023]) – FAS (Population 1 [NATALEE ITT])

	Ribociclib plus AI (N=2,549)	AI (N=2,552)
Number of events, n (%)	204 (8.0)	256 (10.0)
Nominal p-value (1-sided)	[redacted]	
HR (95% CI)	0.749 (0.623, 0.900)	

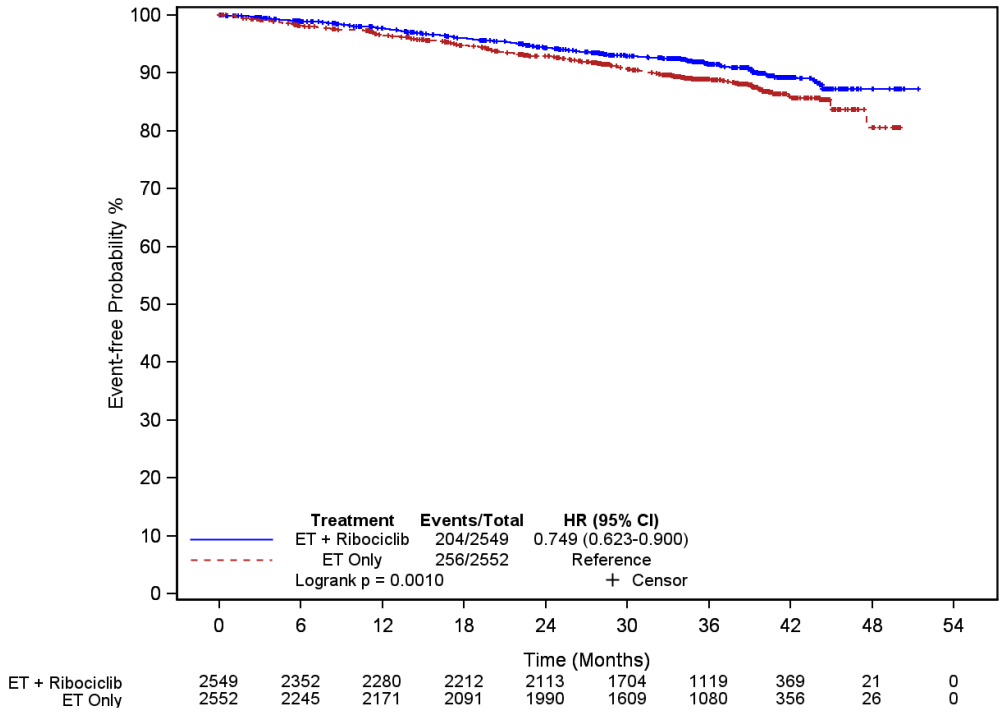
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; DDFS: distant disease-free survival; FAS: full analysis set; HR: hazard ratio; NE: not estimable; PA: primary pre-planned analysis of iDFS.
Source: Novartis Data on File (NATALEE Clinical Study Report Primary Pre-Planned Analysis of iDFS).[92]

Table 20: Summary of DDFS in NATALEE (April 2024 data cut) – FAS (Population 1 [NATALEE ITT])

	Ribociclib plus AI (N=2,549)	AI (N=2,552)
Number of events, n (%)	240 (9.4)	311 (12.2)
p-value (1-sided)[a]	<0.0001	
HR (95% CI)	0.715 (0.604, 0.847)	
3-year DDFS rate, % (95% CI)	91.6 [redacted]	89.2 [redacted]
4-year DDFS rate, % (95% CI)	89.4 [redacted]	84.9 [redacted]

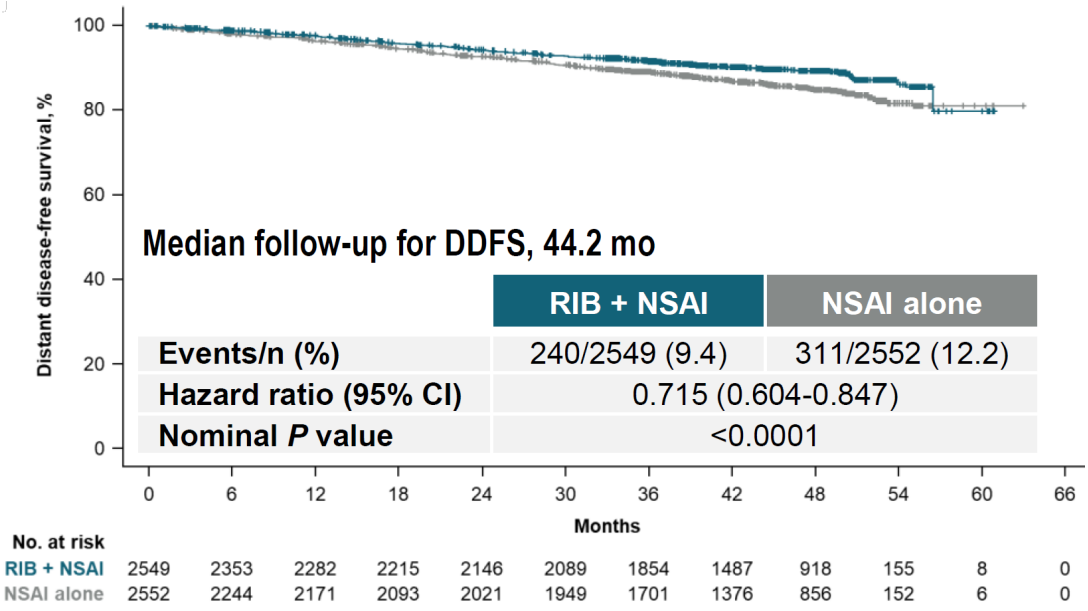
Footnotes: [a] 1-sided p-value for log-rank test stratified by premenopausal women and men vs postmenopausal women, anatomic stage group II vs anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs no) and North America/Western Europe/Oceania vs rest of world.
Hazard rate in group ribociclib plus AI vs hazard rate in group AI is computed using the Cox proportional hazards model with treatment as a single covariate and premenopausal women and men vs postmenopausal women, anatomic stage group II vs anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs no) and North America/Western Europe/Oceania vs rest of world as stratification factors. The group AI is the reference in the hazard ratio calculation.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; DDFS: distant disease-free survival; FA: final iDFS analysis; FAS: full analysis set; HR: hazard ratio; NE: not estimable.
Source: Novartis Data on File (NATALEE Clinical Study Report April 2024 Data Cut: Table 3-3).[79]

Figure 12: Kaplan-Meier plot for DDFS in NATALEE (PA [July 2023]) – FAS (Population 1 [NATALEE ITT])



Footnotes As only AI therapies were received in the NATALEE trial, the "ET" component of the intervention and comparator arm represents AI.
p-value from stratified log-rank test is one-sided.
Abbreviations: CI: confidence interval; DDFS: distant disease-free survival; ET: endocrine therapy; FAS: full analysis set; HR: hazard ratio; PA: primary pre-planned analysis of iDFS.
Source: Novartis Data on File (NATALEE Clinical Study Report Primary Pre-Planned Analysis of iDFS: Figure 4.2-2).[92]

Figure 13: Kaplan-Meier plot for DDFS in NATALEE (April 2024 data cut) – FAS (Population 1 [NATALEE ITT])



Abbreviations: CI: confidence interval; DDFS: distant disease-free survival; ET: endocrine therapy; FAS: full analysis set; HR: hazard ratio; mo: months; NSAI: non-steroidal aromatase inhibitor.
Source: Fasching *et al.* (2024).[93]

Overall survival

At both the PA (July 2023) and the April 2024 data cuts of the NATALEE trial for Population 1 (NATALEE ITT), an early trend in OS was observed in favour of ribociclib plus AI compared with AI

Table 21 and Table 22 present a summary of OS in the FAS (Population 1 [NATALEE ITT]) at the PA (July 2023) and the April 2024 data cut, respectively. At the PA (July 2023), there had been a total of 84/2,549 (3.3%) OS events in the ribociclib plus AI arm, and 88/2,552 (3.4%) in the AI arm. At the April 2024 data cut, this had increased to 105/2,549 (4.1%) and 121/2,552 (4.7%) OS events for the ribociclib plus AI arm and the AI arm, respectively.

In both data cuts, the trend for OS observed for patients in the ribociclib plus AI arm was positive. Notably, the OS HR for the ribociclib plus AI arm compared with the AI arm improved from 0.892 (95% CI: 0.661, 1.203; [redacted]) at the PA (July 2023) to 0.827 (95% CI: 0.636, 1.074; one-sided stratified log-rank test p-value=0.0766) leading to the potential for a continuing (improving) trend in OS at later data cuts. Such a hypothesis is supported by evidence from the advanced or metastatic breast cancer setting where the OS benefit continued to increase with further follow up (see Section B.2.11.1).[94]

OS distribution in NATALEE was estimated using the Kaplan-Meier method. The OS distributions for the PA (July 2023) and the April 2024 data cut are presented in Figure 14 and Figure 15, respectively.

Table 21: Summary of OS in NATALEE (PA [July 2023]) – FAS (Population 1 [NATALEE ITT])

	Ribociclib plus AI (N=2,549)	AI (N=2,552)
Number of events, n (%)	84 (3.3)	88 (3.4)
Nominal p-value (1-sided)	[redacted]	
HR (95% CI)	0.892 (0.661, 1.203)	

Abbreviations: AI: aromatase inhibitor; CI: confidence interval; FAS: full analysis set; HR: hazard ratio; NE: not estimable; OS: overall survival; PA: primary pre-planned analysis of iDFS.
Source: Novartis Data on File (NATALEE Clinical Study Report Primary Pre-Planned Analysis of iDFS: Table 4.2-1).[92]

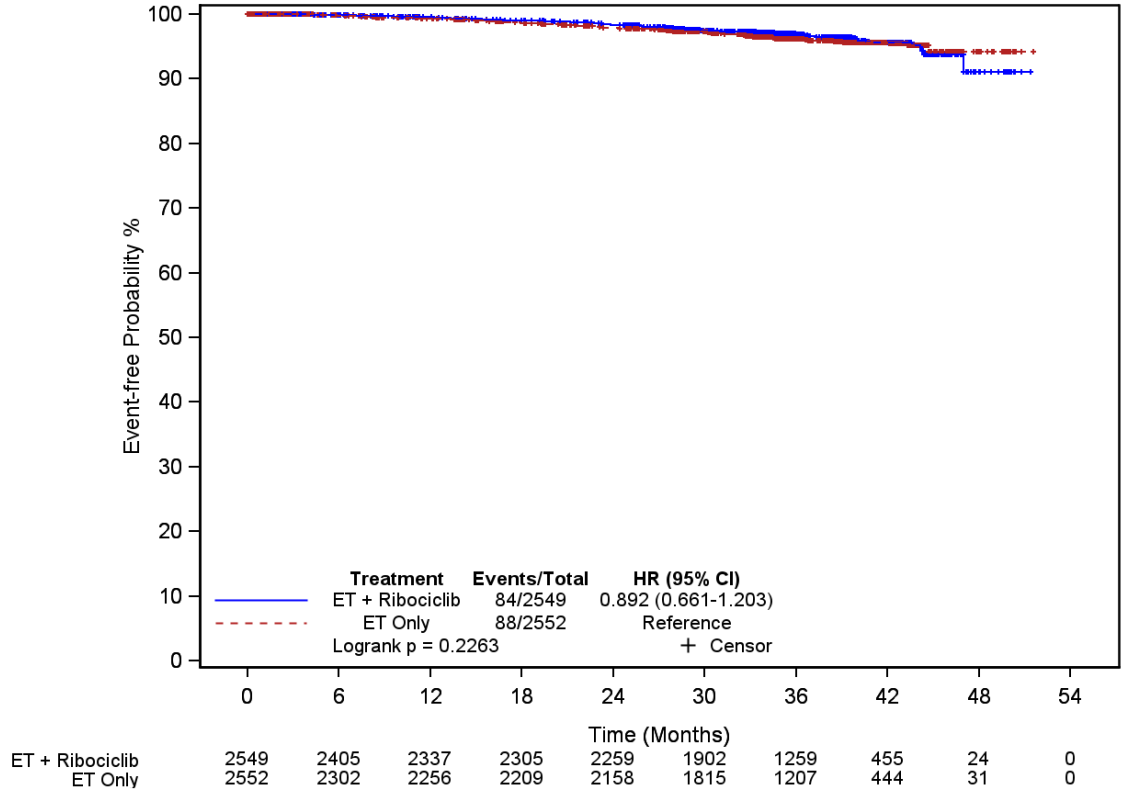
Table 22: Summary of OS in NATALEE (April 2024 data cut) – FAS (Population 1 [NATALEE ITT])

	Ribociclib plus AI (N=2,549)	AI (N=2,552)
Number of events, n (%)	105 (4.1)	121 (4.7)
p-value (1-sided)[a]	0.0766	
HR (95% CI)	0.827 (0.636, 1.074)	
3-year OS rate, % (95% CI)	96.8 [redacted]	96.0 [redacted]
4-year OS rate, % (95% CI)	95.0 [redacted]	94.2 [redacted]

Footnotes: [a] 1-sided p-value for log-rank test stratified by premenopausal women and men vs postmenopausal women, anatomic stage group II vs anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs no) and North America/Western Europe/Oceania vs rest of world.
Hazard rate in group ribociclib plus AI vs hazard rate in group AI is computed using the Cox proportional hazards model with treatment as a single covariate and premenopausal women and men vs postmenopausal

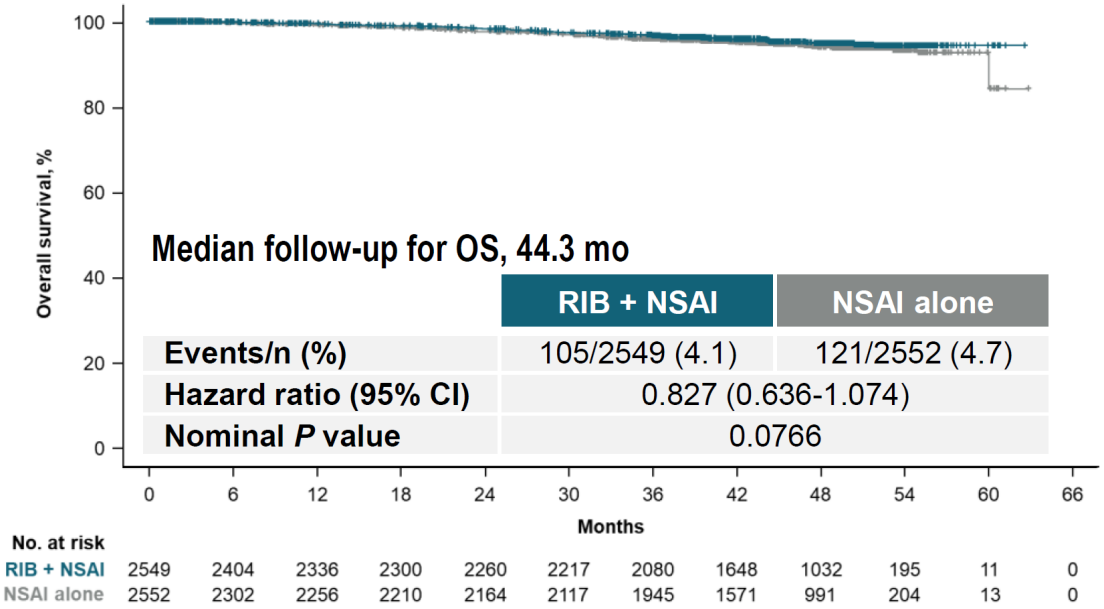
women, anatomic stage group II vs anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs no) and North America/Western Europe/Oceania vs rest of world as stratification factors. The group AI is the reference in the hazard ratio calculation.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; FAS: full analysis set; HR: hazard ratio; NE: not estimable; OS: overall survival.
Source: Novartis Data on File (NATALEE Clinical Study Report April 2024 Data Cut: Table 3-6).[79]

Figure 14: Kaplan-Meier plot for OS in NATALEE (PA [July 2023]) – FAS (Population 1 [NATALEE ITT])



Footnotes: As only AI therapies were received in the NATALEE trial, the "ET" component of the intervention and comparator arm represents AI.
p-value from stratified log-rank test is one-sided.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; ET: endocrine therapy; FAS: full analysis set; HR: hazard ratio; OS: overall survival; PA: primary pre-planned analysis for iDFS.
Source: Novartis Data on File (NATALEE Clinical Study Report Primary Pre-Planned Analysis of iDFS: Figure 4.2-3).[92]

Figure 15: Kaplan-Meier plot for OS in NATALEE (April 2024 data cut) – FAS (Population 1 [NATALEE ITT])



Abbreviations: CI: confidence interval; ET: endocrine therapy; FAS: full analysis set; HR: hazard ratio; OS: overall survival; mo: months; NSAI: non-steroidal aromatase inhibitor.
Source: Fasching *et al.* (2024).[93]

B.2.5.3 Exploratory endpoints

Results from the exploratory analyses at IA3 (January 2023) listed in Table 5 can be found in the IA3 Clinical Study Report.[28] Results from the exploratory analysis of distant recurrence-free survival at the April 2024 data cut are located in Appendix P.

B.2.5.4 Patient-reported outcomes

Four HRQoL questionnaires were used to capture PROs at baseline and at scheduled assessments in NATALEE: the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Specific (EORTC QLQ-BR23), EuroQoL-5 Dimensions (EQ-5D) questionnaire and the hospital anxiety and depression scale (HADS).

The EORTC QLQ-C30 is an internationally validated and widely used measure designed to assess the HRQoL of cancer patients participating in clinical trials.[95] The 30-item measure considers the global health status, and the physical, role, emotional, cognitive, and social functioning of patients, as well as common cancer symptoms experienced by patients. A higher overall QLQ-C30 summary score indicates better HRQoL.[95] The EORTC QLQ-BR23 is a widely used breast cancer-specific questionnaire used to evaluate breast cancer patients' QoL. It utilises five multi-item scales to assess body image, sexual functioning, systemic therapy side effects, breast symptoms, and arm symptoms, as well as single items to assess sexual enjoyment, future perspective and being upset by hair loss.[96]

The EQ-5D is a standardised measure of health status; specifically, the EQ-5D-5L comprises five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), and each dimension has five response levels of severity. The EQ-5D-5L includes a visual analogue scale (VAS) which elicits an individual's rating of their own overall current health using a scale from 1

(the worst health you can imagine) to 100 (the best health you can imagine).[97]

The HADs is a measure of anxiety and depression. The scale comprises seven questions on anxiety, and seven questions on depression. A score out of 21 is calculated for both sets of questions (which should be scored separately); scores of less than 7 indicate non-cases, while scores of 8–10, 11–14, and 15–21 represent mild, moderate, and severe cases, respectively.[98]

PROs were not assessed at the PA (July 2023), nor the April 2024 data cut. Results from the physical functioning sub-scale of the EORTC QLQ-C30 and VAS scores of the EQ-5D-5L from IA3 (January 2023) are instead presented in this section. All other PROs from IA3 (January 2023) are presented in Appendix N.

Overall completion rates for PROs during the treatment period were comparable between both treatment arms. At baseline, PRO data were collected from [redacted] patients [redacted] in the ribociclib plus AI arm vs [redacted] patients [redacted] in the AI arm. At IA3 (January 2023), data were collected for [redacted] patients with a completed end of treatment visit ([redacted]) in the ribociclib plus AI arm vs [redacted] out of [redacted] patients ([redacted]) in the AI arm.

Physical functioning of EORTC QLQ-C30

At IA3 (January 2023) of the NATALEE trial in Population 1 (NATALEE ITT) in general, the EORTC QLQ-C30 physical functioning of patients treated with ribociclib plus AI was similar to that of patients treated with AI (Table 23). Mean baseline physical functioning scores from the EORTC QLQ-C30 were well balanced between the treatment arms: [redacted] (on a scale of 0 to 100) in both the ribociclib plus AI and AI arms. Physical functioning scores were [redacted] between the two treatment arms throughout the study, with [redacted] at any post-baseline timepoint through to end of treatment; there was a [redacted] in physical functioning (i.e., [redacted]) scores for patients in both treatment arms post-baseline These PRO results demonstrate that the addition of ribociclib to AI (compared with AI) does [redacted] patient HRQoL throughout the course of treatment.

Table 23: Physical functioning score of EORTC QLQ-C30 in NATALEE (IA3 [January 2023]) – FAS (Population 1 [NATALEE ITT])

	Ribociclib plus AI N=2,549				AI N=2,552			
PRO	**# Patients with PRO measure at time point**	**Mean**	**SD**	**Change from baseline**	**# Patients with PRO measure at time point**	**Mean**	**SD**	**Change from baseline**
Physical functioning score of EORTC QLQ-C30								
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 13 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 25 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 37 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 49 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 61 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 73 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 85 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 97 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 121 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 145 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 169 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 193 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: Baseline is defined as the last PRO assessment on or prior to randomisation
Abbreviations: AI: aromatase inhibitor; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer quality of life questionnaire; FAS: full analysis set; PRO: patient reported outcome; SD: standard deviation.
Source: Novartis Data on File (NATALEE Clinical Study Report IA3: Table 11–19).[28]

Figure 16: Summary of change from baseline in physical functioning score of EORTC QLQ-C30 questionnaire in NATALEE (IA3 [January 2023]) – FAS (Population 1 [NATALEE ITT])

Footnotes: As only AI therapies were received in the NATALEE trial, the "ET" component of the intervention and comparator arm represents AI.
The time profile provides the average estimates for the change from baseline for the interval from baseline up to the respective cycle as estimated from general linear model (GLM) adjusted by stratification factors at randomisation. Time Point: BL = Baseline, C4D1 = Week 13 Day 1, C7D1 = Week 25 Day 1, C10D1 = Week 37 Day 1, C13D1 = Week 49 Day 1, C16D1 = Week 61 Day 1, C19D1 = Week 73 Day 1, C22D1 = Week 85 Day 1, C25D1 = Week 97 Day 1, C31D1 = Week 121 Day 1, C37D1 = Week 145 Day 1, C43D1 = Week 169 Day 1, 14 = End of Treatment.
Abbreviations: ET: endocrine therapy; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer quality of life questionnaire; EOT: end of treatment; FAS: full analysis set; SEM: standard error of the mean.
Source: Novartis Data on File (NATALEE Clinical Study Report IA3: Figure 11–8).[28]

EQ-5D-5L-VAS

At IA3 (January 2023) of the NATALEE trial in Population 1 (NATALEE ITT) analysis of mean change from baseline of VAS scores of the EQ-5D-5L indicated no meaningful difference between treatment arms over time.

Table 24: Summary of change from baseline in EQ-5D-5L VAS scores in NATALEE (IA3 [January 2023]) – FAS (Population 1 [NATALEE ITT])

	Ribociclib plus AI (N=2,549)				AI (N=2,552)			
PRO	**# Patients with PRO measure at time point**	**Mean**	**SD**	**Change from baseline**	**# Patients with PRO measure at time point**	**Mean**	**SD**	**Change from baseline**
EQ-5D-5L VAS scores								
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 13 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 25 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 37 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 49 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 61 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 73 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 85 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 97 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 121 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 145 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 169 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 193 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: Baseline is defined as the last PRO assessment on or prior to randomisation
Abbreviations: AI: aromatase inhibitor; EQ-5D-5L: EQ-5D-5L VAS: EuroQol 5 Dimension 5 Level Visual Analogue Scale; FAS: full analysis set; PRO: patient reported outcome; SD: standard deviation.
Source: Novartis Data on File (NATALEE Clinical Study Report IA3: Table 14.2–7.1).[28]

Figure 17: Summary of change from baseline in EQ-5D-5L VAS scores in NATALEE (IA3 [January 2023]) – FAS (Population 1 [NATALEE ITT])

Footnotes: As only AI therapies were received in the NATALEE trial, the "ET" component of the intervention and comparator arm represents AI.
The time profile provides the average estimates for the change from baseline for the interval from baseline up to the respective cycle as estimated from general linear model (GLM) adjusted by stratification factors at randomisation.
Time Point: BL = Baseline, C4D1 = Week 13 Day 1, C7D1 = Week 25 Day 1, C10D1 = Week 37 Day 1, C13D1 = Week 49 Day 1, C16D1 = Week 61 Day 1, C19D1 = Week 73 Day 1, C22D1 = Week 85 Day 1, C25D1 = Week 97 Day 1, C31D1 = Week 121 Day 1, C37D1 = Week 145 Day 1, C43D1 = Week 169 Day 1, 14 = End of Treatment.
Abbreviations: EOT: end of treatment; EQ-5D-5L VAS: EuroQol 5 Dimension 5 Level Visual Analogue Scale; ET: endocrine therapy; FAS: full analysis set.
Source: Novartis Data on File (NATALEE Clinical Study Report IA3: Figure 14.2–2.6).[28]

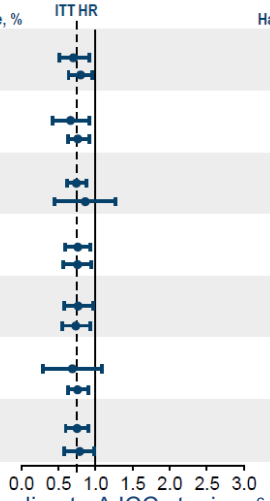
B.2.6 Subgroup analysis

Subgroup analyses were conducted for the primary endpoint of iDFS in the NATALEE trial for Population 1 (NATALEE ITT). Results of these subgroup analyses at the April 2024 data cut demonstrate a consistent treatment effect for ribociclib plus AI vs AI across stratification factors of menopausal status, anatomic stage, prior chemotherapy, geographic region, Ki-67 status, nodal status and prior ET (Figure 18).

Subgroup analysis results for iDFS in the node-positive and node negative subgroups specifically are presented in Section B.2.6.1, as requested in the NICE final scope.

Figure 18: Forest plot of iDFS by stratum in NATALEE (April 2024 data cut) (Population 1 [NATALEE ITT])

Subgroup	RIB + NSAI Events/n	RIB + NSAI 4-y iDFS rate, %	NSAI alone Events/n	NSAI alone 4-y iDFS rate, %	Hazard ratio	95% CI
Menopausal status						
Men and premenopausal women	99/1125	90.7	137/1132	85.3	0.677	0.523-0.877
Postmenopausal women	164/1424	86.8	203/1420	82.2	0.760	0.619-0.933
AJCC stage						
Stage II	62/1012	93.9	96/1034	89.6	0.644	0.468-0.887
Stage III	200/1527	84.3	244/1512	78.4	0.737	0.611-0.888
Prior CT						
Yes	238/2249	88.2	309/2245	83.0	0.715	0.604-0.846
No	25/300	90.7	31/307	87.5	0.827	0.488-1.401
Region						
North America/Western Europe/Oceania	151/1563	88.9	195/1565	84.2	0.726	0.587-0.898
Rest of world	112/986	88.0	145/987	82.6	0.722	0.564-0.925
Ki-67 status[a]						
Ki-67 ≤20%	106/1199	89.9	142/1236	85.9	0.737	0.573-0.948
Ki-67 >20%	113/920	86.3	149/937	80.4	0.709	0.555-0.905
Nodal status[b,c]						
N0	23/285	92.1	38/328	87.0	0.666	0.397-1.118
N1-N3	240/2261	88.0	301/2219	83.0	0.731	0.617-0.866
Prior ET						
Yes	176/1830	89.2	227/1807	84.5	0.718	0.589-0.874
No	87/719	86.7	113/745	81.4	0.752	0.568-0.994



Footnotes: [a] From archival tumour tissue. [b] Nodal status classification according to AJCC staging. [c] Nodal status is from the worst stage derived per surgical specimen or at diagnosis.
Abbreviations: AJCC: American Joint Committee on Cancer; CI: confidence interval; ET: endocrine therapy; FAS; full analysis set; HR: hazard ratio: iDFS: invasive disease-free survival; NA: North America; NSAI: non-steroidal aromatase inhibitor; O: Oceania; RIB: ribociclib; ROW: rest of world; WE: Western Europe.
Source: Fasching *et al.* (2024).[93]

B.2.6.1 Subgroup analyses in Population 2 (NATALEE node-positive high-risk) and Population 3 (NATALEE node-negative high-risk)

As specified in the NICE final scope, subgroup analysis results from the NATALEE trial are presented for patients in Population 2 (NATALEE node-positive high-risk) and Population 3 (NATALEE node-negative high-risk).

At the PA (July 2023), in Population 2 (NATALEE node-positive high-risk), the iDFS HR for ribociclib plus AI vs AI was 0.759 (95% CI: 0.631, 0.912), indicating a 24.1% risk reduction in iDFS. In Population 3 (NATALEE node-negative high-risk), the iDFS HR for ribociclib plus AI vs AI was 0.723 (95% CI: 0.412, 1.268), indicating a 27.7% relative reduction in the risk of invasive cancer recurrence, new cancer events or death. The results across Population 2 (NATALEE node-positive high-risk) and Population 3 (NATALEE node-negative high-risk) are comparable to the 25.1% relative reduction in risk of an iDFS event observed in the FAS population (Population 1 [NATALEE

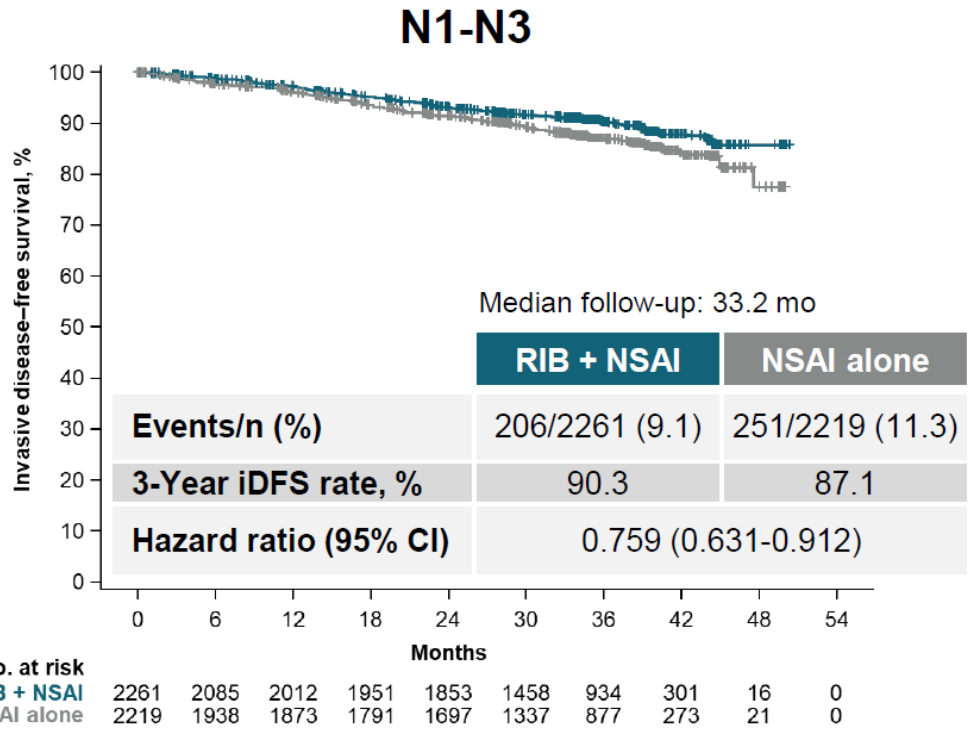
ITT]), at the PA (July 2023).

At the April 2024 data cut, the iDFS HR for ribociclib plus AI vs AI had improved to 0.731 (95% CI: 0.617, 0.866) in Population 2 (NATALEE node-positive high-risk), representing 26.9% relative reduction in risk of an iDFS event, and to 0.666 (95% CI: 0.397, 1.118) in Population 3 (NATALEE node-negative high-risk), representing a 33.4% relative reduction in risk of an iDFS event. As before, the results across Population 2 (NATALEE node-positive high-risk) and Population 3 (NATALEE node-negative high-risk) are similar to the 28.5% relative reduction in risk of an iDFS event observed across the FAS (Population 1 [NATALEE ITT]), at the April 2024 data cut.

Taken together, the iDFS improvement for ribociclib plus AI vs AI was consistent across both subgroups by nodal status (Population 2 [NATALEE node-positive high-risk] and Population 3 [NATALEE node-negative high-risk]) and with the full population (Population 1 [NATALEE ITT]).

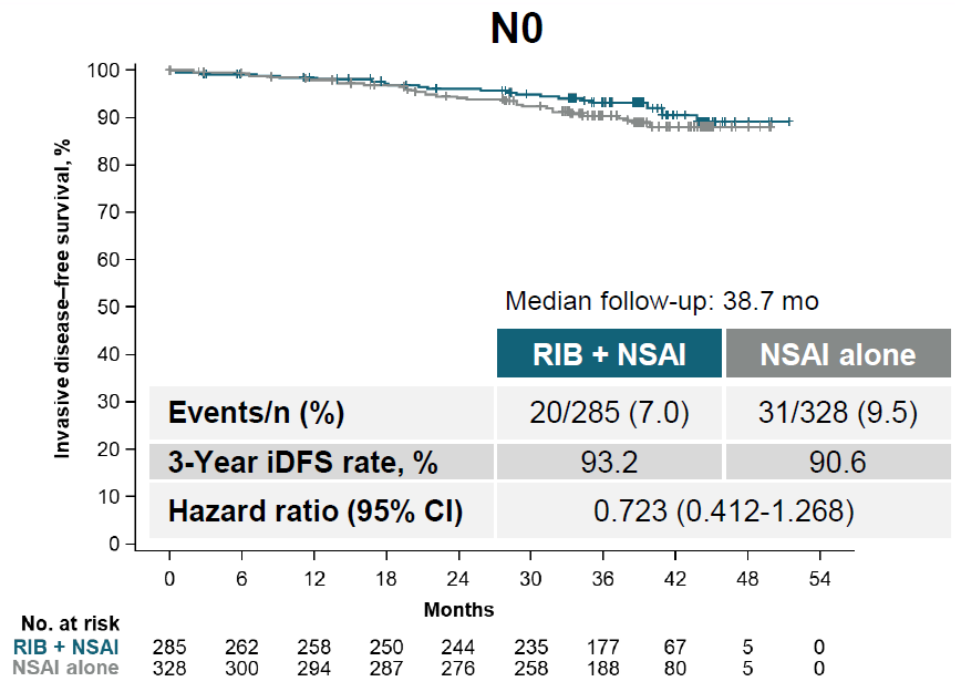
The iDFS distributions as of the PA (July 2023), estimated using the Kaplan-Meier method in both Population 2 (NATALEE node-positive high-risk) and Population 3 (NATALEE node-negative high-risk) are presented in Figure 19 and Figure 20, respectively. The equivalent distributions from the April 2024 data cut are presented in Figure 21 and Figure 22, respectively.

Figure 19: Kaplan-Meier plot for iDFS in NATALEE (PA [July 2023]) – Population 2 (NATALEE node-positive high-risk)



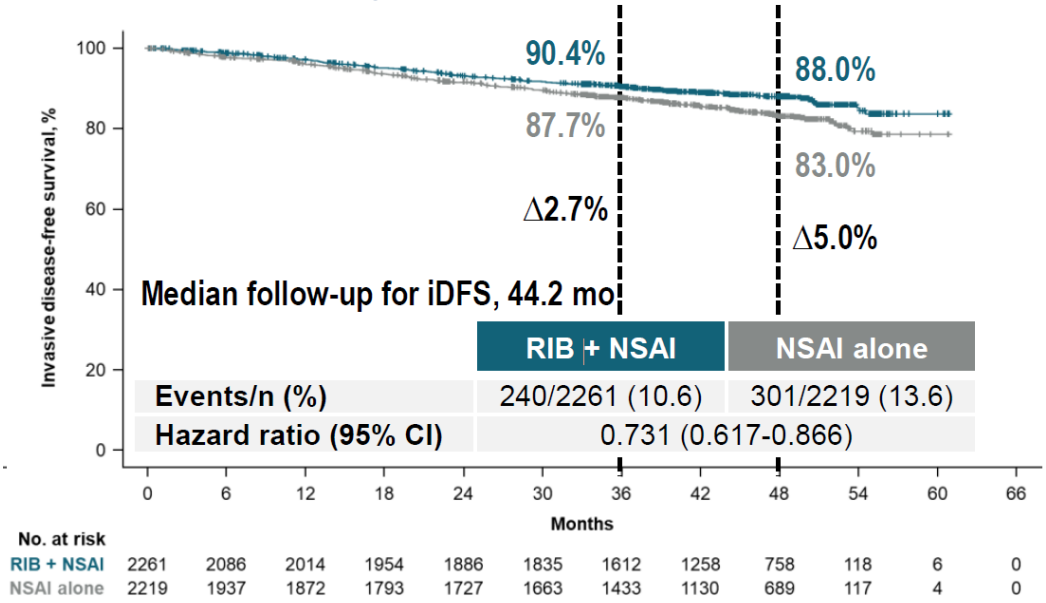
Footnotes: p-value from stratified log-rank test is one-sided.
Abbreviations: CI: confidence interval; HR: hazard ratio; iDFS: invasive disease-free survival; NSAI: non-steroidal aromatase inhibitor; PA: primary pre-planned analysis of iDFS; RIB: ribociclib.
Source: Hortobagyi *et al.* (2023).[99]

Figure 20: Kaplan-Meier plot for iDFS in NATALEE (PA [July 2023]) – Population 3 (NATALEE node-negative high-risk)



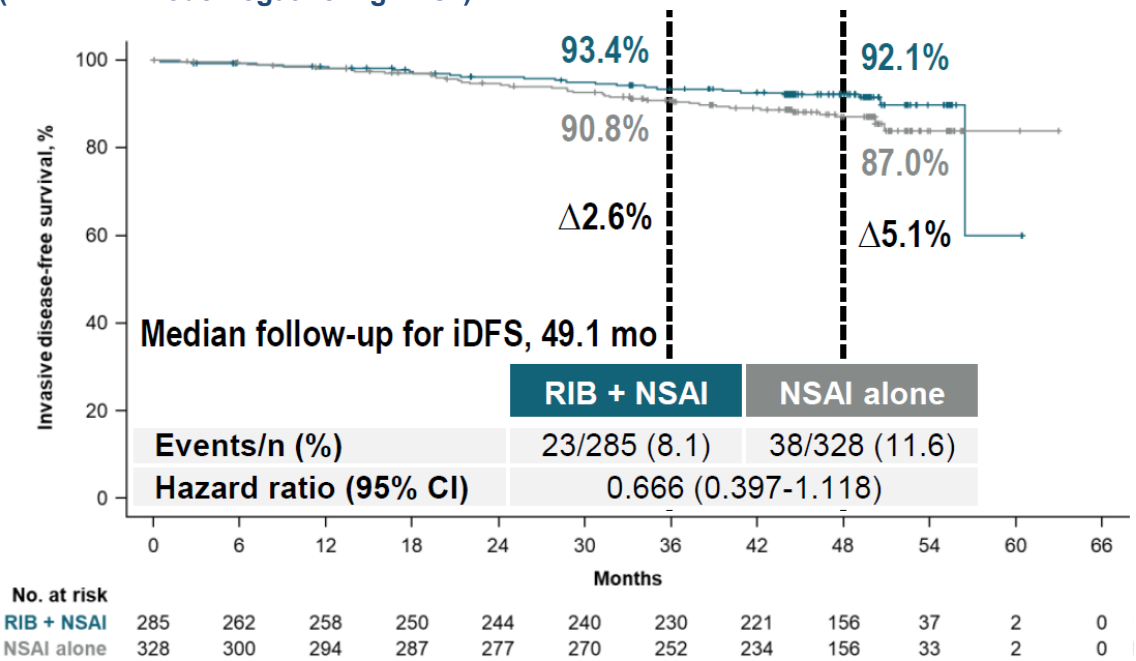
Footnotes: p-value from stratified log-rank test is one-sided.
Abbreviations: CI: confidence interval; HR: hazard ratio; iDFS: invasive disease-free survival; NSAI: non-steroidal aromatase inhibitor; PA: primary pre-planned analysis of iDFS; RIB: ribociclib.
Source: Hortobagyi *et al.* (2023).[99]

Figure 21: Kaplan-Meier plot for iDFS in NATALEE (April 2024 data cut) – Population 2 (NATALEE node-positive high-risk)



Footnotes: p-value from stratified log-rank test is one-sided.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; iDFS: invasive disease-free survival; NSAI: non-steroidal aromatase inhibitor; RIB: ribociclib.
Source: Fasching *et al.* (2024).[93]

Figure 22: Kaplan-Meier plot for iDFS in NATALEE (April 2024 data cut) – Population 3 (NATALEE node-negative high-risk)



Footnotes: p-value from stratified log-rank test is one-sided.
Abbreviations: CI: confidence interval; HR: hazard ratio; iDFS: invasive disease-free survival; mo: months; NSAI: non-steroidal aromatase inhibitor; RIB: ribociclib.
Source: Fasching *et al.* (2024).[93]

B.2.7 Meta-analysis

This section is not applicable as no pooling of trials was undertaken.

B.2.8 Indirect and mixed treatment comparisons

As discussed in Section B.1.1, abemaciclib plus ET and ET are considered relevant comparators to ribociclib plus AI in Population 4 (node-positive high-risk eligible for abemaciclib). The criteria used to define Population 4 has been described previously in Section B.1.1, and is in line with the NICE TAG for abemaciclib plus ET in TA810.[6] As ribociclib plus AI has not been directly compared in a head-to-head trial vs abemaciclib plus ET or vs ET in Population 4 (node-positive high-risk eligible for abemaciclib), an ITC was required to enable their comparison in this subgroup.

B.2.8.1 Identification and selection of relevant studies

As described in Section B.2.1, an SLR was conducted in March 2023, and subsequently updated in October 2023 and June 2024, to identify all relevant clinical evidence for the efficacy and safety of ribociclib plus AI and other relevant treatment options for patients with HR+/HER2– EBC.

Overall, 195 records, reporting on 52 unique studies, were included in the SLR and subsequently considered for inclusion within the ITC based on the PICO criteria detailed in Table 25. The ITC PICO criteria considered studies for ribociclib plus AI, abemaciclib plus ET and ET that reported outcomes for iDFS, OS and safety in Population 4 (node-positive high-risk eligible for abemaciclib)

i.e., patients with node-positive HR+/HER2– EBC who are at high risk of recurrence and eligible for abemaciclib.

Of the 52 studies included in the SLR, 48 studies were relevant to the decision problem (one was identified for ribociclib plus AI, one for abemaciclib plus ET and 46 for ET). The remaining studies were for palbociclib and everolimus, which were not relevant to the decision problem or the ITC.

Table 25: PICO framework for the ITC for Population 4 (node-positive high-risk eligible for abemaciclib)

PICO criteria	Characteristics
Population	• Adult (age ≥18 years) men and women with node-positive HR+/HER2– EBC, with pathological tumour involvement: ○ ≥4 ipsilateral ALNs, or ○ 1–3 ALNs with either: ○ Grade 3 disease or ○ primary tumour size ≥5 cm
Intervention	• Ribociclib plus AI
Comparators†	• Abemaciclib plus ET (letrozole, anastrozole, exemestane, or tamoxifen) • ET
Outcomes	Efficacy • iDFS • OS Safety • Grade 3 or higher TEAEs • Incidence must be ≥5%

Abbreviations: EBC: early breast cancer; ET: endocrine therapy; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; iDFS: invasive disease-free survival; ITC: indirect treatment comparison; OS: overall survival; TEAE: treatment-emergent adverse event.

Of the 48 identified studies reporting on the intervention or comparators of interest, only one study included the population of relevance for the ITC (i.e., Population 4 [node-positive high-risk eligible for abemaciclib]): the monarchE trial. The definition of high risk of recurrence within monarchE is presented in Table 26. As shown, patients in monarchE were enrolled in two cohorts, each with different criteria used to define high-risk characteristics. Only Cohort 1 (N=5,120) of the monarchE trial was considered further within the ITC, as this corresponds to the population in which abemaciclib plus ET has received a positive recommendation from NICE (TA810).[6] Cohort 2 (N=517) was comprised of patients who were node-positive and had a Ki-67 score ≥20%; these patients do not match the NICE-approved population for abemaciclib plus ET and were therefore not considered further in the ITC.

In summary, in addition to NATALEE, data for which were available as individual patient data (IPD) from Novartis, only one trial was identified for inclusion within the ITC for Population 4 (node-positive high-risk eligible for abemaciclib): monarchE (specifically Cohort 1). Data for abemaciclib plus ET were therefore derived from monarchE (Cohort 1), based on publications summarising the results and methods of the monarchE trial at the aggregate level. Data for ribociclib plus AI and ET were derived from the NATALEE trial (for which individual patient data [IPD] were available). The AI arm

of the NATALEE trial was used to inform the efficacy of ET and is therefore referred to as 'ET' hereafter in this section.

Table 26: Assessment parameters used in monarchE to define patients classified as having HR+/HER2– EBC at high risk of recurrence

Study name	Risk type[a]	Cohort	Assessment parameters					
			Nodes	Tumour size	Histologic grade	Ki-67	Age	Other
monarchE	High	Cohort 1	4+; 1–3	5+ cm (1–3 nodes)	3 (1–3 nodes)	N/A	N/A	N/A
		Cohort 2	1–3	N/A	N/A	≥20%		

Footnotes: [a] As reported by the authors
Abbreviations: EBC: early breast cancer; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; Ki-67: antigen Kiel 67; N/A: not applicable.

B.2.8.2 Feasibility assessment

A feasibility assessment was conducted to assess the feasibility of conducting an anchored ITC between ribociclib plus AI and abemaciclib plus ET and ET, and to determine the most appropriate ITC approach considering the evidence sources available.

A detailed comparison of the NATALEE trial and Cohort 1 of the monarchE trial was conducted and is presented in Appendix D. A summary of the key differences between the trials that may influence an ITC has been provided below.

Study design

The feasibility assessment determined that an unanchored MAIC was the most robust approach for comparing ribociclib plus AI vs abemaciclib plus ET and ET in the population of interest (Population 4 [node-positive high-risk eligible for abemaciclib]. Details of the feasibility assessment are summarised in Appendix D. Briefly, the approach for the primary MAIC analysis was determined based on the following findings from the feasibility assessment:

- Disconnected evidence network: The control arms in NATALEE and monarchE were comprised of different therapies and did not represent a common comparator through which to form a connected network. In addition, no other trials were identified that could facilitate a connected evidence network between the two trials. As such, an anchored ITC was not feasible.
- The NATALEE control arm comprised AIs only (i.e., letrozole, anastrozole). The monarchE control arm was ET consisting of AIs (exemestane) and tamoxifen. As discussed in Section B.3.11, there is a wealth of evidence demonstrating that AIs are more effective than tamoxifen at reducing disease recurrence in EBC (see Appendix M.1). A TLR identified a number of published meta-analyses and clinical trials comparing the efficacy of tamoxifen vs AIs as monotherapy.[100-104] The results of these do not support the assumption that the control arms in monarchE and NATALEE could be considered equivalent, and instead demonstrate that AIs are more effective than tamoxifen in reducing disease recurrence.

As such, it was not considered possible to construct a connected evidence network between Cohort 1 of the monarchE trial to the NATALEE trial. Any ITCs of NATALEE vs Cohort 1 of monarchE therefore needed to be unanchored, or 'naïve' comparisons.

Eligibility criteria

The monarchE trial was focused on a subset of EBC patients classified as being at high risk of recurrence according to several criteria, including the number of nodes and/or the tumour size and disease grade (see Section B.1.1). The population of the NATALEE trial was defined based on disease stage and therefore includes a broader population of patients than the monarchE trial. As such, given IPD were available from the NATALEE trial, it was considered feasible to match patients enrolled in the NATALEE trial who had the high risk of recurrence and nodal status characteristics required for eligibility in the monarchE trial. This population from the NATALEE trial is referred to in this submission as the 'NATALEE-selected' population, and is used to inform the comparison of ribociclib plus AI vs abemaciclib plus ET, and ribociclib plus AI vs ET in Population 4 (node-positive high-risk eligible for abemaciclib). After selecting patients in NATALEE who would meet eligibility criteria for monarchE, residual differences in baseline characteristics were still observed between the two trials (see below).

Baseline characteristics

A comparison of baseline characteristics between Cohort 1 of monarchE and the NATALEE-selected population was undertaken to see if there were any significant differences that would bias a comparison of results. A comparison of baseline characteristics demonstrated that the trials were well-balanced for many of the reported characteristics at baseline, although standardised mean differences (SMDs) exceeded 20% for proportions of patients with Ki-67 index ≥20%, those residing in geographic region reported as "other" (i.e., not North America, Europe, or Asia), those whose ethnicity was not Hispanic or Latino, those with stage IIA or IIIA, and patients with prior neoadjuvant chemotherapy (see Appendix D.6), which further supported the use of a MAIC approach over an unadjusted analysis.

Outcome definitions

The definitions of iDFS and OS were consistent between the monarchE and NATALEE trials. AE definitions were also consistent between the monarchE and NATALEE trials and were assessed using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0.

Conclusion

Based on the comparison of NATALEE and monarchE presented above, it was considered most appropriate to conduct an unanchored MAIC of ribociclib plus AI vs ET informed by the NATALEE-selected population (the AI arm of the NATALEE trial was used to inform the efficacy of ET) and vs abemaciclib plus ET informed by Cohort 1 of monarchE. This approach allowed for the use of population-adjustment methods to provide a more robust comparison over an unadjusted and unanchored ITC.

Two commonly used population-adjusted ITC approaches are MAICs and simulated treatment

comparisons (STCs). Both approaches can be used to adjust for differences in population baseline characteristics between trials of interest, allowing for a more robust ITC than conventional methods, especially with unanchored ITCs.[105] A key disadvantage of STCs is that they can be biased when using outcomes based on non-linear regression, such as time-to-event outcomes.[106] A key disadvantage of the MAIC approach is that weighting with small sample sizes may result in very low effective sample sizes which can undermine the power of a comparison. However, considering the very large sample size of the NATALEE trial and the time-to-event outcomes being compared, a MAIC was considered the more appropriate option.

Analyses conducted

In summary, an unanchored MAIC of ribociclib plus AI vs ET in the NATALEE-selected population and vs abemaciclib plus ET in Cohort 1 population of monarchE was considered the most appropriate analysis to assess comparative efficacy in Population 4 (node-positive high-risk eligible for abemaciclib). The methodology and results of the primary MAIC analysis are presented below.

B.2.8.3 Methodology

An overview of the MAIC methodology for the primary MAIC analysis is presented in the following sections.

Summary of data cut-off dates used for each trial

The primary MAIC analysis used the latest available data for the NATALEE (April 2024 data cut) and monarchE trials where possible. There were differences between the median follow-up times for the latest available data from NATALEE, with median study follow-up of [redacted] months, compared with monarchE Cohort 1, which had a median follow-up of 54.0 months.[79, 107] Durations of follow-up for the NATALEE and monarchE studies are summarised in Table 27.

Table 27: Summary of NATALEE and monarchE trial data used in the primary MAIC analysis

Trial	Trial population	Trial arms	Data cut	Median follow-up (months)	Source
monarchE	Cohort 1 (n=5,120)	Abemaciclib plus ET (n=2,555)	July 2023	54.0	Rastogi *et al.* (2024) [107]
NATALEE	Selected[a] (n=2,946)	Ribociclib plus AI (n=1,658)	April 2024	[redacted]	April 2024 data cut (Novartis Data on file)
		AI (n=1,649)[b]			

Footnotes: [a] Based on selected NATALEE dataset to match criteria for patients at high-risk of recurrence in monarchE (Cohort 1); [b] The AI arm of the NATALEE trial was used to inform the efficacy of ET.
Abbreviations: AI: aromatase inhibitor; MAIC: matching-adjusted indirect comparison.

Selection of variables for adjustment

An underlying assumption for an unanchored MAIC is that all potential effect modifiers and prognostic factors are accounted for. As such, given that only aggregate data were available for monarchE, patient baseline demographic and disease characteristics used in the calculation of the MAIC weights for the primary ITC analysis included all of the characteristics reported in the

published reports of the monarchE trial that could be calculated from the NATALEE IPD, as follows:

- Age (mean)
- Age (% ≤65 years)
- Sex (% female)
- Race (White, Asian, other)
- Ethnicity (Hispanic or Latino vs not)
- Weight, kg (mean)
- BMI, kg/m^2 (mean)
- Region (North America/Europe vs Asia vs other)
- Pathological diagnosis term
- HR status (ER+, ER–, PR+, PR–)
- Menopausal status (pre-menopausal vs post-menopausal)
- Positive ALNs (0 vs 1–3 vs 4+)
- Histopathology at diagnosis (Grade 1 vs Grade 2 vs Grade 3)
- Ki-67 index (<20 vs ≥20)
- ECOG prognostic score (0, 1, 3+)
- TNM Stage (I–III [A–C])
- Tumour side (left, right, bilateral)
- Prior chemotherapies (adjuvant, neo-adjuvant, both, neither)
- Prior radiotherapy (yes vs no)

Any missing values in the NATALEE IPD were imputed by randomly assigning values such that the distribution of imputed values was approximately equal to that for the non-missing values.

Three clinical experts (two of which practice in the UK) were interviewed to determine which of these characteristics were known to be prognostic factors and effect modifiers in EBC, by varying degrees of influence (see Appendix Q.1). Table 28 shows the clinical expert ranking of all reported variables by levels of “high importance”, “low importance”, and “not important”. The yellow rows indicate characteristics for which there was a consensus among clinicians of “high importance” as a prognostic factor for efficacy in EBC. The blue rows correspond to the factors which were deemed to have some level of importance in EBC prognosis by at least one clinical expert (i.e., at least one clinical expert indicated low importance as a prognostic factor for efficacy in EBC). The white rows correspond to the factors for which the clinical experts did not indicate as having important prognostic influence in EBC.

Table 28: Clinical expert ranking of prognostic factors

Characteristic	Clinical expert 1	Clinical expert 2	Clinical expert 3
Pathological diagnosis term	High importance	High importance	High importance
HR Status, %	High importance	High importance	High importance
Positive ALNs, %	High importance	High importance	High importance
Histopathology at diagnosis, %	High importance	High importance	High importance
TNM Stage, %	High importance	High importance	High importance
Pathologic tumour size (cm), %	High importance	High importance	High importance
Ki-67 Index, %	High importance	Low importance	High importance
Menopausal status, %	Low importance	Low importance	Low importance
Age, years	Low importance	Not important	Low importance
Weight, kg	Low importance	Not important	Low importance
BMI, kg/m2	Low importance	Not important	Low importance
Prior chemotherapy, %	Low importance	Not important	Low importance
Prior radiotherapy, %	Low importance	Not important	Low importance
ECOG PS	Low importance	Low importance	Not important
Tumour side	Not important	Low importance	Not important
Female, %	Not important	Not important	Not important
Race, %	Not important	Not important	Not important
Ethnicity, %	Not important	Not important	Not important
Region, %	Not important	Not important	Not important

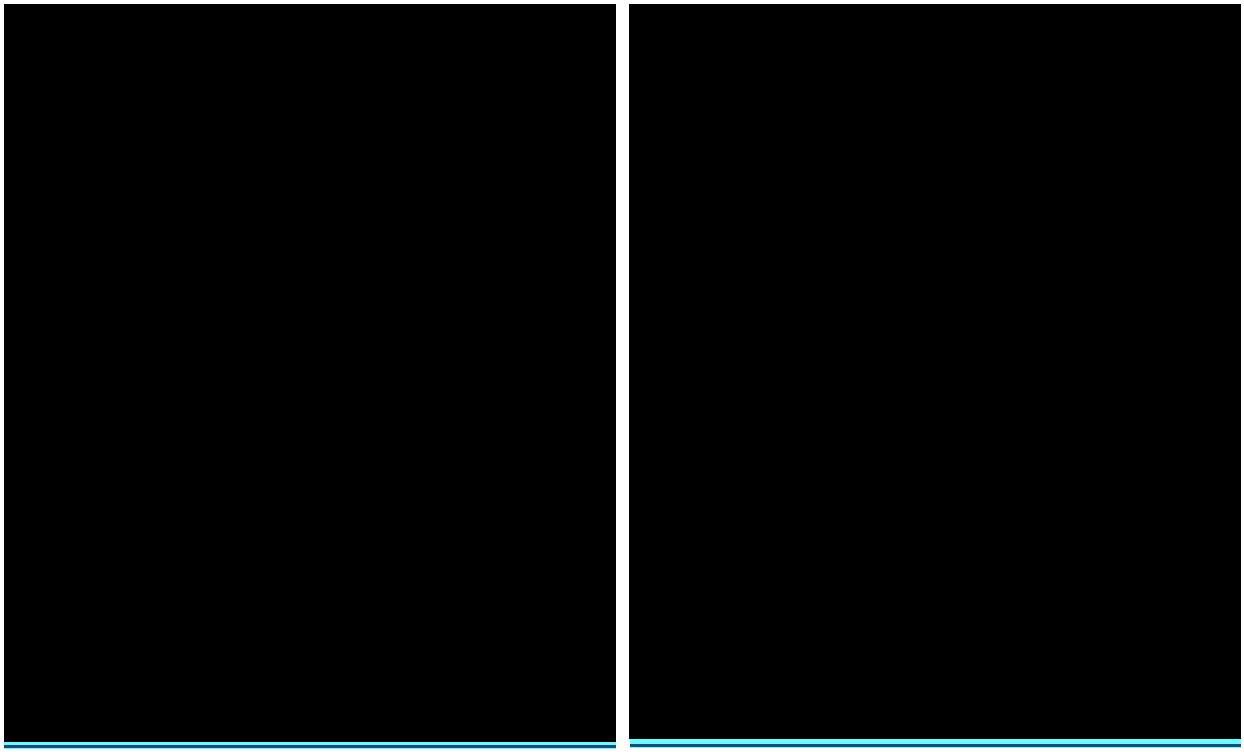
Footnotes: Blue rows indicate characteristics considered important by at least one clinician, yellow rows indicate characteristics considered highly important by at least one clinician
Abbreviations: ALNs: axillary lymph nodes; BMI: body mass index; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: hormone receptor; TNM: tumour, node and metastases.

Identification of treatment effect modifiers

Statistical tests were conducted to identify treatment effect modifiers and prognostic factors using iDFS IPD from NATALEE. Treatment effect modification was assessed for each characteristic based on interaction tests using Cox proportional hazards (PH) regression of patient-level failure time data for the iDFS outcome.

Cox PH regression models were specified with covariates for treatment, a given characteristic, and the interaction of treatment arm with the characteristic. The p-values for the interaction terms were then used to assess whether the treatment effect with ribociclib plus AI was modified based on an alpha of 0.05. As shown in Figure 23, the p-values were >0.05 for all characteristics, suggesting that there is no evidence to demonstrate that the treatment effect of ribociclib plus AI on iDFS is modified by any of these characteristics.

Figure 23: Forest plot of iDFS HRs for potential treatment effect modifiers from NATALEE, with interaction tests



Abbreviations: ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; iDFS: invasive disease-free survival; ITT: intention-to-treat; PR: progesterone receptor.

Interaction tests for baseline characteristics have also been conducted in the literature for prespecified subgroups of the monarchE trial, as reported by Johnston *et al.* (2023).[108] This study reported the p-value for the interaction test of treatment and primary tumour size (<2 cm, 2–5 cm, ≥5cm) to be 0.044, which suggests that the treatment effect for abemaciclib plus ET on iDFS is modified by tumour size (see Table 29). Findings for all other reported interaction tests of treatment effect of abemaciclib plus ET on iDFS in monarchE suggested no treatment effect modification based on an alpha of 0.05.[108]

Identification of prognostic factors

Prognostic factors were assessed based on stratified Kaplan-Meier analyses of iDFS from NATALEE, irrespective of treatment. The log-rank test was used to assess whether there was a difference in survival among the curves, with a statistically significant finding (i.e., a p-value <0.05) suggesting that the characteristic is prognostic. All quantitative assessments for treatment effect modification and prognostic factors are summarised in Table 29.

Table 29: Summary of quantitative tests for treatment effect modifier and prognostic factors: iDFS

Characteristic	Interaction test p-value (treatment effect modifiers)		Log-rank p-value (prognostic factors)
	NATALEE	monarchE	NATALEE
Menopause (pre, post)	0.3934	0.120	0.1839
Stage (IIA, IIB, IIIA, IIIB, IIIC)	0.8178	0.350	**0.0000**
Female/Male	0.9664	NR	0.8753
Prior neo-adjuvant chemotherapy (Yes, No)	0.3206	0.610	**0.0000**
Prior adjuvant chemotherapy (Yes, No)	0.3368	0.610	**0.0018**
Tumour side (left, right)	0.9803	NR	0.8034
Prior radiation therapy (Yes, No)	0.5105	NR	0.1062
Race (Asian, White, Other)	0.4004	0.340	0.3004
Region (North America/Europe, Asia, Other)	0.2543	0.600	0.3748
Ethnicity (Hispanic/Latino, Other)	0.2543	NR	0.4869
Age, years (median = 53)	0.6236	0.350	**0.0100**
Age category (<65, ≥65 years)	0.4439	NR	**0.0112**
ECOG (0, 1)	0.5778	0.088	0.0640
ER status (+, -)	0.9491	NR	0.1855
PR status (+, -)	0.4033	0.260	**0.0003**
Nodes (1–3, ≥4)	0.5278	0.660	**0.0000**
Tumour size, cm (<2, 2–5, >5)	0.7392	**0.044**	**0.0008**
Histologic grade (1, 2, 3)	0.7392	0.750	**0.0152**
Ki-67 Index (<20%, ≥20%)	0.5337	NR	0.1957
Histologic subtype (ductal, lobular, tubular)	0.3917	NR	0.8487
BMI, kg/m^2 (median=26.4)	0.2552	NR	0.6333
Weight, kg (median=70)	0.2894	NR	0.7195

Footnotes: Bold font indicates significant interaction at an alpha of 0.05.
Abbreviations: BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; ER: oestrogen receptor; iDFS: invasive disease-free survival; NR: not reported; PR: progesterone receptor.

Primary MAIC analysis

The primary MAIC analysis adjusted for all of the available characteristics shown in Table 29, consistent with guidance for unanchored MAICs from NICE DSU TSD 18.[109] Adjusting for factors that are not prognostic does not bias the unanchored comparison. The primary MAIC analysis therefore adjusted for all variables that were indicated as having prognostic influence by clinical experts, all variables that modified treatment effect based on the interaction tests, all variables that were prognostic based on stratified log-rank tests, as well as all variables without evidence of prognostic influence.

Sensitivity analysis

A sensitivity analysis was conducted that adjusted for all baseline characteristics that were considered to have some prognostic value according to the clinical experts (i.e., indicated as low importance or high importance by at least one clinical expert) and all variables that with statistically significant findings for interaction tests and/or tests of prognostic factors) (blue and yellow rows of Table 30).

Table 30 provides an overview of the factors adjusted for in the primary MAIC analysis and the sensitivity analysis.

Table 30: Adjustment factors included in MAIC analyses

Characteristic	Prognostic		Effect modifier [a]		Included in analysis	
	Clinical expert ranking	Log-Rank Test	NATALE E	monarch E	Primary [b]	Sensitivity analysis[c]
Pathological Dx Term	High	—	—	—	✓	✓
HR Status	High	Significant	—	—	✓	✓
Lymph Nodes (n)	High	Significant	—	—	✓	✓
Histopathology at Dx	High	Significant	—	—	✓	✓
TNM Stage	High	Significant	—	—	✓	✓
Tumour Size (cm)	High	Significant	—	Significant	✓	✓
Ki-67 Index	High	—	—	—	✓	✓
Menopausal status	Low	—	—	—	✓	✓
Age, years	Low	Significant	—	—	✓	✓
Weight, kg	Low	—	—	—	✓	✓
BMI, kg/m2	Low	—	—	—	✓	✓
Prior chemotherapy	Low	Significant	—	—	✓	✓
Prior Radiotherapy	Low	—	—	—	✓	✓
ECOG PS	Low	—	—	—	✓	✓
Tumour side	Low	—	—	—	✓	✓
Female	—	—	—	—	✓	
Race	—	—	—	—	✓	
Ethnicity	—	—	—	—	✓	
Region	—	—	—	—	✓	

Footnotes: "—" indicates not important (per clinician interview) or not statistically significant at alpha=0.05 (if statistical test). [a] Based on p-value for interaction test; [b] All available characteristics; [c] Any importance based on clinician interviews and/or statistically significant based on statistical test.
Abbreviations: BMI: body mass index; Dx: diagnosis; ECOG PS: Eastern Cooperative Oncology Group performance status; HR: hormone receptor; MAIC: matching-adjusted indirect comparison; SA: sensitivity analysis; TNM: tumour, node, metastasis.

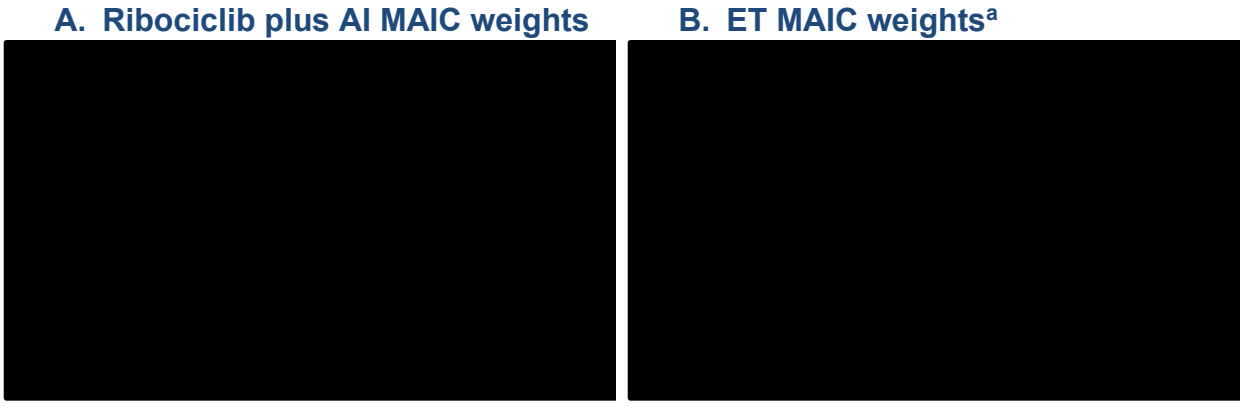
B.2.8.4 MAIC weights

MAIC weights were estimated using the MAIC package in R which is an adaptation of sample code from the NICE DSU TSD 18.[109] Further details on the population-adjustment methods are provided in Appendix D.7 and Appendix D.8.

In the primary MAIC analysis, weighting was conducted using all patient baseline characteristics outlined in Table 29. In the weighting process, each patient was given a weight representing the inverse of the odds of being in the NATALEE trial vs being in the monarchE trial. This means that patients who were less likely to be among the abemaciclib plus ET trial population (given its characteristics) were assigned more weight in the analysis and vice versa. The impact of reweighting is that there is less statistical information in the reweighted trial data, which is reflected in the effective sample size (ESS). A small ESS can indicate that the estimated rebalancing weights are highly variable (creating extreme weights) due to a lack of population overlap between two populations. This can result in little statistical power to detect differences between treatments and estimates of relative treatment effect may become inflated/unstable as they depend heavily on a small number of individuals.[110]

Histograms of the estimated weights for each treatment arm are shown in Figure 24; descriptive statistics of the estimated MAIC weights are shown in
Table 31. Most of the estimated weights for both treatment arms are below 5.0. There were 22 patients in the NATALEE-selected population with an estimated weight of 0.0. The maximum weight values in the ribociclib plus AI arm and the ET arms (the AI arm of NATALEE was used to inform the efficacy of ET, and is therefore referred to as 'ET' hereafter in this section) were [redacted] and [redacted], respectively. After weighting, the ESS for the ribociclib plus AI and ET arms were [redacted] and [redacted], respectively, constituting an estimated reduction of [redacted]% to [redacted]% from the selected sample size in each arm. Given that the ESS was still relatively large after weighting, use of the MAIC adjusting for all available characteristics was considered appropriate.

Figure 24: Primary MAIC analysis: histogram of MAIC weights (NATALEE-selected population)



Footnotes: [a]The AI arm of the NATALEE trial was used to inform the efficacy of ET.
Abbreviations: AI: aromatase inhibitor; ET: endocrine therapy; MAIC: matching-adjusted indirect comparison.

Table 31: Primary MAIC analysis: summary of MAIC weights (NATALEE-selected population)

Characteristic	Ribociclib plus AI	ET[a]
N	[redacted]	[redacted]
ESS	[redacted]	[redacted]
Percent change in sample size	[redacted]	[redacted]
Max weight	[redacted]	[redacted]

Footnotes: [a] The AI arm of the NATALEE trial was used to inform the efficacy of ET.
Abbreviations: AI: aromatase inhibitor; ESS: effective sample size; ET: endocrine therapy; MAIC: matching-adjusted indirect comparison.

The patient baseline characteristics after patient selection and after MAIC weighting are shown in Table 32. After weighting, standardised mean differences (SMD) between patient baseline characteristics of the weighted NATALEE population and Cohort 1 of the monarchE trial were relatively small or zero.

Table 32: Primary MAIC analysis for Population 4 (node-positive high-risk eligible for abemaciclib): patient baseline characteristics before and after weighting

Characteristic	MonarchE (Cohort 1)		NATALEE-selected, unweighted		NATALEE-selected, weighted		SMD	
	Abemaciclib plus ET (N=2,555)	ET (N=2,565)	Ribociclib plus AI (N=1,658)	ET (N=1,649)	Ribociclib plus AI (ESS=448)	ET (ESS=453)	monarchE Cohort 1 abemaciclib plus ET vs NATALEE-selected, weighted ribociclib plus AI	monarchE Cohort 1 ET vs NATALEE-selected, weighted ET
Age, years								
Mean	52.2	52.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<65, %	84.1%	85.4%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥65, %	15.9%	14.6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, %	99.2%	99.2%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, %								
Asian	24.7%	23.9%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White	70.6%	71.0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	4.7%	5.1%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity, %								
Hispanic or Latino	8.0%	8.9%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	92.0%	91.1%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	0.0%	0.0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Region, %								
North America/Europe	51.8%	51.9%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	MonarchE (Cohort 1)		NATALEE-selected, unweighted		NATALEE-selected, weighted		SMD	
	Abemaciclib plus ET (N=2,555)	ET (N=2,565)	Ribociclib plus AI (N=1,658)	ET (N=1,649)	Ribociclib plus AI (ESS=448)	ET (ESS=453)	monarchE Cohort 1 abemaciclib plus ET vs NATALEE-selected, weighted ribociclib plus AI	monarchE Cohort 1 ET vs NATALEE-selected, weighted ET
Asia	20.4%	20.4%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	27.8%	27.7%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight, kg, mean	71.3	71.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m2, mean	27.2	27.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pathological diagnosis term, %								
Invasive ductal breast carcinoma	67.3%	68.7%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Invasive lobular breast carcinoma	13.9%	13.1%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tubular breast carcinoma	0.1%	0.2%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	18.7%	18.1%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR status, %								
ER+	99.3%	99.3%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ER–	0.5%	0.6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ER missing	0.2%	0.0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PR+	86.4%	86.8%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PR–	10.5%	10.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PR Missing	3.1%	2.7%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	MonarchE (Cohort 1)		NATALEE-selected, unweighted		NATALEE-selected, weighted		SMD	
	Abemaciclib plus ET (N=2,555)	ET (N=2,565)	Ribociclib plus AI (N=1,658)	ET (N=1,649)	Ribociclib plus AI (ESS=448)	ET (ESS=453)	monarchE Cohort 1 abemaciclib plus ET vs NATALEE-selected, weighted ribociclib plus AI	monarchE Cohort 1 ET vs NATALEE-selected, weighted ET
Menopausal status, %								
Pre-menopausal	43.7%	43.1%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-menopausal	56.3%	56.9%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Positive axillary lymph nodes, %								
0	0.2%	0.2%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1–3	34.2%	34.6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥4	65.6%	65.1%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Histopathology at diagnosis, %								
Grade 1	7.3%	7.4%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2	46.2%	46.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3	41.6%	40.9%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Assessed/Missing	4.9%	5.1%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS								
0	85.4%	83.7%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	14.5%	16.1%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3,4, and Missing	0.1%	0.1%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tumour side								

Characteristic	MonarchE (Cohort 1)		NATALEE-selected, unweighted		NATALEE-selected, weighted		SMD	
	Abemaciclib plus ET (N=2,555)	ET (N=2,565)	Ribociclib plus AI (N=1,658)	ET (N=1,649)	Ribociclib plus AI (ESS=448)	ET (ESS=453)	monarchE Cohort 1 abemaciclib plus ET vs NATALEE-selected, weighted ribociclib plus AI	monarchE Cohort 1 ET vs NATALEE-selected, weighted ET
Left	51.8%	49.8%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Right	46.6%	49.1%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bilateral	1.6%	1.1%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pathologic tumour size (cm), %								
<2	26.5%	25.6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2–5	48.3%	49.8%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥5	23.5%	23.6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	1.8%	1.0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ki-67 Index, %								
<20	37.0%	37.7%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥20	39.8%	38.4%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	23.2%	23.9%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TNM stage, %								
IA	0.0%	0.0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IB	0.0%	0.0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IIA	9.0%	9.7%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IIB	11.0%	11.2%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IIIA	40.0%	39.7%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	MonarchE (Cohort 1)		NATALEE-selected, unweighted		NATALEE-selected, weighted		SMD	
	Abemaciclib plus ET (N=2,555)	ET (N=2,565)	Ribociclib plus AI (N=1,658)	ET (N=1,649)	Ribociclib plus AI (ESS=448)	ET (ESS=453)	monarchE Cohort 1 abemaciclib plus ET vs NATALEE-selected, weighted ribociclib plus AI	monarchE Cohort 1 ET vs NATALEE-selected, weighted ET
IIIB	3.8%	3.3%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IIIC	35.8%	36.1%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	0.4%	0.2%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior chemotherapy, %								
Neoadjuvant	36.5%	36.3%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjuvant	58.7%	58.6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
None	4.8%	5.1%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior radiotherapy, %								
Prior radiotherapy, %	96.0%	96.1%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: The AI arm of the NATLEE trial was used to inform the efficacy of ET.
Abbreviations: AI: aromatase inhibitor; BMI: body mass index; CDK4/6: cyclin-dependent kinases 4/6; ECOG PS: Eastern Cooperative Oncology Group performance status; ER: oestrogen receptor; Ki-67: antigen Kiel-67; ET: endocrine therapy; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; SMD: standardised mean difference; TNM: tumour-node-metastasis.

B.2.8.5 Primary MAIC analysis results

Invasive disease-free survival (iDFS)

HRs for the primary MAIC analysis comparison of iDFS in Population 4 (node-positive high-risk eligible for abemaciclib) are shown in Table 33, both before and after matching, for ribociclib plus AI vs abemaciclib plus ET and ET. HRs <1 favour ribociclib plus AI. Further details of each comparison are provided below.

Table 33: Summary of primary MAIC analysis for iDFS in Population 4 (node-positive high-risk eligible for abemaciclib)

	Before matching, unweighted comparison HR (95% CI)	After matching, MAIC HR (95% CI)
Ribociclib plus AI vs abemaciclib plus ET	[redacted]	[redacted]
Ribociclib plus AI vs ET[a]	[redacted]	[redacted]

Footnotes: [a] The AI arm of the NATLEE trial was used to inform the efficacy of ET.
Abbreviations: AI: aromatase inhibitors; CI: confidence interval; HR: hazard ratio; iDFS; invasive disease-free survival; ITC: indirect treatment comparison; MAIC: matching adjusted indirect comparison.

Ribociclib plus AI vs abemaciclib plus ET (Population 4 [node-positive high-risk eligible for abemaciclib])

Before matching, the HR for the comparison of iDFS between ribociclib plus AI and abemaciclib plus ET in Population 4 (node-positive high-risk eligible for abemaciclib) was [redacted] and not statistically significant at the 95% confidence level (p-value=[redacted]). After matching, the HR for the comparison of iDFS was [redacted] for ribociclib plus AI vs abemaciclib plus ET, and also not statistically significant (p-value=[redacted].

The Kaplan-Meier figure for the comparison of iDFS between ribociclib plus AI and abemaciclib plus ET in Population 4 (node-positive high-risk eligible for abemaciclib), both before and after matching, is shown in Figure 25. The unweighted iDFS Kaplan-Meier curves for ribociclib plus AI are almost indistinguishable from those for abemaciclib plus ET until approximately [redacted]. The weighted Kaplan-Meier curve for ribociclib plus AI is just slightly increased above abemaciclib plus ET throughout the NATALEE follow-up period.

Figure 25: Kaplan-Meier plot for the primary MAIC analysis of iDFS with ribociclib plus AI vs abemaciclib plus ET (high-risk population eligible for abemaciclib)

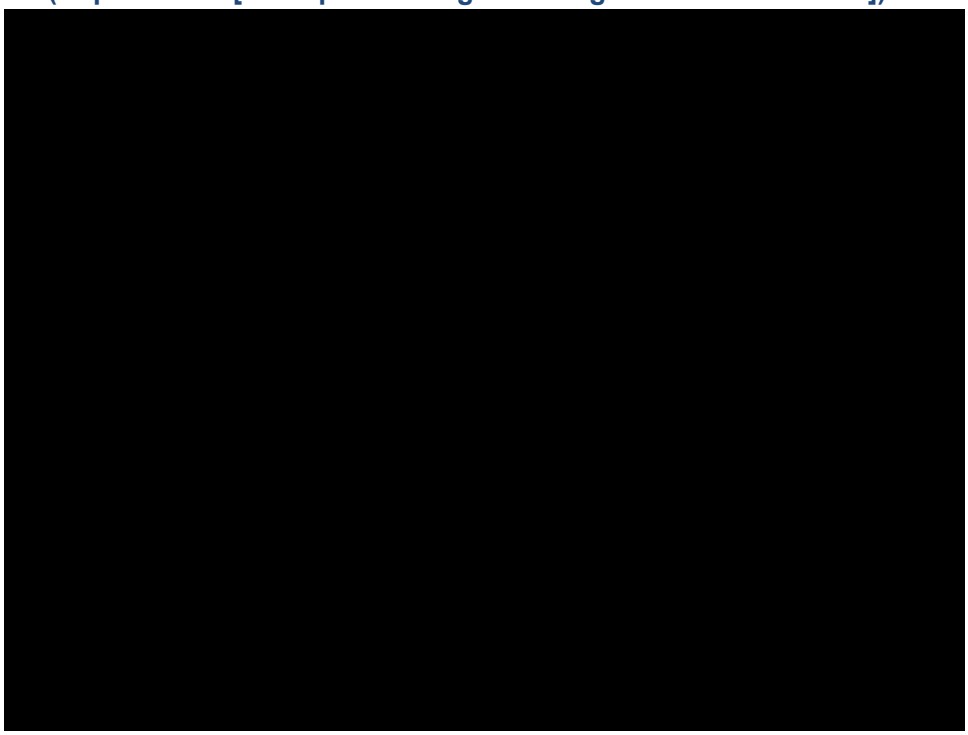
Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; HR: hazard ratio; iDFS: invasive disease-free survival; K-M: Kaplan-Meier; MAIC: matching-adjusted indirect comparison; PH; proportional hazard; wgt: weight.

Ribociclib plus AI vs ET (Population 4 [node-positive high-risk eligible for abemaciclib])

Both before and after matching, ribociclib plus AI was associated with statistically significantly improved iDFS vs ET in Population 4 (node-positive high-risk eligible for abemaciclib). The before matching [redacted] the after matching HR was [redacted]

The Kaplan-Meier figure for the comparison of iDFS between ribociclib plus AI and ET in Population 4 (node-positive high-risk eligible for abemaciclib), both before and after matching, is shown in Figure 26. The weighted Kaplan-Meier curves for the ribociclib plus AI and ET arms shift slightly upwards compared with the unweighted Kaplan-Meier curves.

Figure 26: Kaplan-Meier plot for primary MAIC analysis of iDFS with ribociclib plus AI vs ET (Population 4 [node-positive high-risk eligible for abemaciclib])



Footnotes: The AI arm of the NATLEE trial was used to inform the efficacy of ET.
Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; iDFS: invasive disease-free survival; MAIC: matching-adjusted indirect comparison; wgt: weight.

Further details of the primary MAIC analysis methodology and results are presented in Appendix D.

Further details of the MAIC sensitivity analysis methodology and results, including the MAIC weights and Kaplan-Meier curves, are also presented in Appendix D. In summary, results from the iDFS MAIC sensitivity analysis were consistent with the primary MAIC analysis, suggesting no statistically significant difference between ribociclib plus AI and abemaciclib plus ET, and a statistically significant difference between ribociclib plus AI and ET.

Overall survival (OS)

HRs for the primary MAIC analysis comparison of OS in Population 4 (node-positive high-risk eligible for abemaciclib) are shown in Table 34 both before and after matching, for ribociclib plus AI vs abemaciclib plus ET and ET. Further details of each comparison are provided below.

Table 34: Summary of primary MAIC analysis for OS (Population 4 [node-positive high-risk eligible for abemaciclib])

	Before matching, unweighted comparison HR (95% CI)	After matching, MAIC HR (95% CI)
Ribociclib plus AI vs abemaciclib plus ET	[redacted]	[redacted]
Ribociclib plus AI vs ET[a]	[redacted]	[redacted]

Footnotes: [a]The AI arm of the NATLEE trial was used to inform the efficacy of ET.
Abbreviations: AI: aromatase inhibitors; CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; ITC: indirect treatment comparison; MAIC: matching-adjusted indirect comparison; OS: overall survival.

Ribociclib plus AI vs abemaciclib plus ET (Population 4 [node-positive high-risk eligible for abemaciclib])

Before matching, the HR for the comparison of OS between ribociclib plus AI and abemaciclib plus ET in Population 4 (node-positive high-risk eligible for abemaciclib) was [redacted]; this difference was not statistically significant at the 95% confidence level (p-value=[redacted]). After matching, the HR for the comparison of OS was [redacted] for ribociclib plus AI vs abemaciclib plus ET; this difference was also not statistically significant (p-value=[redacted].

The Kaplan-Meier figure for the comparison of OS between ribociclib plus AI and abemaciclib plus ET in Population 4 (node-positive high-risk eligible for abemaciclib), both before and after matching, is shown in Figure 27. The weighted Kaplan-Meier OS curve for ribociclib plus AI is slightly above Kaplan-Meier OS for abemaciclib plus ET until approximately [redacted], at which point the curves cross.

Figure 27: Kaplan-Meier plot for the primary MAIC analysis of OS with ribociclib plus AI vs abemaciclib plus ET (Population 4 [node-positive high-risk eligible for abemaciclib])

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; HR: hazard ratio; K-M: Kaplan-Meier; MAIC: matching-adjusted indirect comparison; OS: overall survival; PH: proportional hazards; wgt: weight.

Ribociclib plus AI vs ET (Population 4 [node-positive high-risk eligible for abemaciclib])

Before matching, the HR for the comparison of OS between ribociclib plus AI and ET in Population 4 (node-positive high-risk eligible for abemaciclib) was [redacted]; this difference was not statistically significant at the 95% confidence level (p-value=[redacted]). After matching, the HR for the comparison of OS was [redacted] for ribociclib plus AI vs abemaciclib plus ET; this difference was also not statistically significant (p-value=[redacted].

The Kaplan-Meier figure for the comparison of OS between ribociclib plus AI and ET in Population 4 (node-positive high-risk eligible for abemaciclib), both before and after matching, is shown in Figure 28. The weighted Kaplan-Meier curves for the ribociclib plus AI and ET arms shift slightly upwards compared with the unweighted Kaplan-Meier curves.

Figure 28: Kaplan-Meier plot for primary MAIC analysis of OS with ribociclib plus AI vs ET (Population 4 [node-positive high-risk eligible for abemaciclib])

Footnotes: The AI arm of the NATLEE trial was used to inform the efficacy of ET.
Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; MAIC: matching-adjusted indirect comparison; OS: overall survival; wgt: weight.

Details of the MAIC sensitivity analysis methodology and results for the OS comparisons, including the MAIC weights and Kaplan-Meier curves, are presented in Appendix D. In summary, results from the OS MAIC sensitivity analysis were consistent with the primary MAIC analysis, suggesting no statistically significant difference between treatments (ribociclib plus AI vs abemaciclib plus ET, or vs ET).

Safety outcomes

A comparison of safety between ribociclib plus AI and abemaciclib plus ET in terms of the emergence of TEAEs within Population 4 (node-positive high-risk eligible for abemaciclib) was conducted for the primary MAIC analysis. ORs and 95% credible intervals (CrIs) for the primary MAIC analysis comparison of TEAEs are shown in Table 35; an OR value <1 favours ribociclib plus AI (i.e., the event is less likely to occur for patients treated with ribociclib plus AI).

Both before and after matching, ribociclib plus AI was associated with statistically significantly reduced odds of diarrhoea (a key symptomatic AE), leukopenia, and lymphopenia, and statistically significantly increased odds of increased alanine aminotransferase and neutropenia vs abemaciclib plus ET in Population 4 (node-positive high-risk eligible for abemaciclib). These results therefore support the approach to include different TEAE rates (and therefore costs) for each therapy in the cost-effectiveness model (see Section B.3.3.5).

Table 35: Summary of primary MAIC analysis for TEAEs with ribociclib plus AI vs abemaciclib plus ET (Population 4 [node-positive high-risk eligible for abemaciclib])

Endpoint	Rate % (95 CI)		Unweighted OR (95% CI)	Weighted OR (95% CI)
	Ribociclib plus AI	Abemaciclib plus ET		
ALT increased	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AI: aromatase inhibitors; ALT: alanine transaminase; CI: confidence interval; ET: endocrine therapy; MAIC: matching-adjusted indirect comparison; OR: odds ratio.

B.2.8.6 Uncertainties in the indirect and mixed treatment comparisons

The above analyses demonstrate that, for the indirect comparison of ribociclib plus AI vs abemaciclib plus ET, the NATALEE-selected population and the Cohort 1 monarchE population had minor differences with respect to the variables included in the analysis before adjustment. After adjustment, the two populations were better aligned and provided a more appropriate basis to compare the outcomes of interest between populations. Nevertheless, the analysis may be limited by unreported prognostic factors that could not be adjusted for in the MAIC weights. Whilst clinical expert opinion has confirmed that all key covariates were adjusted for in the analysis, there is a risk of unreported or unobserved confounding factors that could not be adjusted for (see Appendix Q.1).

Secondly, patients eligible for inclusion in the monarchE trial constitute a subset of those eligible for the NATALEE trial. Selection of the NATALEE population for inclusion in the MAIC resulted in a ~[redacted]% reduction in the original trial sample size for each treatment arm and may constitute a break in randomisation from the original NATALEE ITT population. Comparison of outcomes may therefore be biased given the smaller patient pool, even smaller ESS (approximately half of the selected pool for the base case), and the lack of a purely randomised set of patients. However, given the ESS still included a large number of patients, with 448 patients for ribociclib plus AI and 453 patients for the ET arm in the primary MAIC analysis, this is not anticipated to impact the reliability of results.

Finally, the Kaplan-Meier curves from the monarchE trial used in the analyses were based on reconstructed IPD. While the Kaplan-Meier curves estimated from the reconstructed data were similar to those reported in the monarchE publications, it is not possible to have them match exactly. Given that these differences are relatively small, they are not likely to materially bias the findings reported here.

In summary, the results of the primary MAIC analysis (that adjusted for all possible baseline characteristics) showed no statistically significant differences in treatment effect in terms of iDFS and OS ribociclib plus AI and abemaciclib plus ET in Population 4 (node-positive high-risk eligible

for abemaciclib). Statistically significant improvements in iDFS, although not OS, were identified between ribociclib plus AI and ET in Population 4 (node-positive high-risk eligible for abemaciclib). The sensitivity analysis (that adjusted for all baseline characteristics that were considered potentially prognostic) showed similar results to the primary MAIC analysis. In terms of safety, ribociclib plus AI was associated with a statistically significantly lower odds of the occurrence of diarrhoea (a key symptomatic AE), leukopenia, and lymphopenia and a statistically significantly greater odds of increased alanine aminotransferase and neutropenia than abemaciclib plus ET.

B.2.9 Adverse reactions

Summary of the safety evidence from the NATALEE trial at the April 2024 data cut

- The safety of ribociclib was evaluated as a secondary endpoint within the NATALEE trial. At the April 2024 data cut, in the ribociclib plus AI arm, [redacted] patients experienced at least one AE, as did [redacted] patients in the AI arm.
- [redacted], [redacted] and [redacted] were the most common treatment emergent AEs (TEAEs) irrespective of causality in the ribociclib plus AI arm.
- Incidences of serious TEAEs were infrequent in both arms [redacted] experienced serious TEAEs that were suspected to be related to study treatment in the ribociclib plus AI arm, and AI arm, respectively.
- TEAEs leading to treatment discontinuation (ribociclib and/or AI) occurred more frequently in the ribociclib plus AI arm in comparison to the AI arm [redacted]
- In total, at the April 2024 data cut, [redacted] had died in the ribociclib plus AI arm; [redacted] died in the AI arm; the most common primary reason for death was disease recurrence/progression [redacted], respectively).
- Safety results from the April 2024 data cut of NATALEE showed that ribociclib plus AI is associated with a predictable and manageable safety profile. No new safety signals or safety concerns were identified; ribociclib-related AEs are well characterised from the advanced or metastatic breast cancer indication, manageable with appropriate intervention, and generally reversible upon treatment adjustment.

For simplicity, only safety results from the April 2024 data cut are presented in the following sections. Safety results from the IA3 (January 2023) and the PA (July 2023) are presented in Appendix N and Appendix O, respectively.

B.2.9.1 Summary of adverse events

A summary of AEs reported during the study at the April 2024 data cut is presented in Table 36. All safety analyses were based on the NATALEE safety set (see Section B.2.4).

At the April 2024 data cut, a total of [redacted] of patients in the ribociclib plus AI arm and [redacted] of patients in the AI arm experienced at least one AE during the study. As might be expected, AEs

in the following categories were reported more frequently in the ribociclib plus AI arm relative to the AI arm.

- AEs suspected to be study-drug related [redacted]
- Serious adverse events (SAEs) suspected to be related to study-drug related [redacted]
- AEs leading to discontinuation [redacted]
- AEs leading to discontinuation suspected to be study-drug related [redacted]
- AEs requiring dose interruption [redacted]
- AEs requiring dose interruption suspected to be study-drug related [redacted]
- AEs requiring additional therapy [redacted]
- AEs requiring additional therapy suspected to be study-drug related [redacted]
- Adverse event of special interest (AESI; [redacted]
- AESI suspected to be study-drug related [redacted]

In total, at the April 2024 data cut, [redacted] had died in the ribociclib plus AI arm and [redacted] had died in the AI arm; the most common primary reason for death was disease recurrence/progression [redacted] respectively). As of the April 2024 data cut, on-treatment deaths (deaths within up to 30 days after 36 months of treatment or earlier treatment discontinuation) had occurred in [redacted] in the ribociclib plus AI arm and [redacted] in the AI arm.

Table 36: Summary of deaths and AE categories in NATALEE (April 2024 data cut) – safety set

	Ribociclib plus AI N=2,526				AI N=2,441			
Category	**All Grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**All Grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
All deaths[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On-treatment deaths[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Suspected to be drug-related	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Suspected to be drug-related	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Suspected to be drug-related	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs requiring dose interruption	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Suspected to be drug-related	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs requiring dose adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Suspected to be drug-related	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs requiring additional therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Suspected to be drug-related	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs of special interest	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Suspected to be drug-related	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a]All deaths including those not considered on-treatment deaths. Includes deaths with cause other than AE. Deaths due to disease progression or other are listed in the All Grades column.
[b]On treatment deaths are defined as occurring on or after treatment start date and up to 30 days after 36 months of treatment or earlier treatment discontinuation. Includes deaths with cause other than AE. Deaths due to disease progression or other are listed in the All Grades column.
Suspected to be drug related refers to any component of study treatment.
Additional therapy includes all non-drug therapy and concomitant medications.
Discontinuation refers to discontinuation of any treatment component.
Subjects are counted once per category at worst toxicity grade in the main category rows, and once per category per toxicity in the related rows.

Abbreviations: AE: adverse event; AI: aromatase inhibitor; NA: not applicable; SAE: serious adverse event.
Source: Novartis Data on File (NATALEE Clinical Study Report April 2024 Data Cut: Table 4-4).[79]

B.2.9.2 Treatment emergent adverse events

Table 37 presents TEAEs (irrespective of causality) in both treatment arms by primary system organ class and maximum grade at the April 2024 data cut. [redacted] were the most common TEAEs (reported in ≥50% of patients; grouped by primary system organ class) with ribociclib plus AI. Musculoskeletal and connective tissue disorders was the only TEAE (grouped by system organ class) reported in in ≥50% of patients in the AI arm (reported in [redacted] of patients receiving AI).

Table 37: AEs, irrespective of causality, by primary system organ class and maximum grade in NATALEE (April 2024 data cut) – safety set

	Ribociclib plus AI N=2,526				AI N=2,441			
System organ class	**All Grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**All Grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
Number of patients with at least one TEAE	[redacted]							
Investigations	[redacted]							
Musculoskeletal and connective tissue disorders	[redacted]							
General disorders and administration site conditions	[redacted]							
Gastrointestinal disorders	[redacted]							
Infections and infestations	[redacted]							
Blood and lymphatic system disorders	[redacted]							
Nervous system disorders	[redacted]							
Skin and subcutaneous tissue disorders	[redacted]							

Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reproductive system and breast disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Endocrine disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Product issues	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Congenital, familial and genetic disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Social circumstances	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: System organ classes are sorted in descending frequency based on frequency in ribociclib plus AI arm.
MedDRA Version 27.0 has been used for reporting
Abbreviations: AE: adverse event; AI: aromatase inhibitor; TEAE: treatment emergent adverse event.
Source: Novartis Data on File (NATALEE Clinical Study Report April 2024 Data Cut: Table 4–5).[79]

AEs as of the April 2024 data cut, irrespective of causality by preferred term and maximum grade are presented in Table 38. [redacted] arthralgia,

[redacted] nausea, headache, fatigue, [redacted] were the most common TEAEs (reported in ≥20% of patients) with ribociclib plus AI. Arthralgia was the only event reported in ≥20% of patients in the AI arm (reported in 44.4% of patients receiving AI).

Table 38: AEs, irrespective of causality by preferred term and maximum grade in NATALEE (at least 2% incidence in either arm) (April 2024 data cut) – safety set

	Ribociclib plus AI N=2,526				AI N=2,441			
Preferred term	**All Grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**All Grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
Number of patients with at least one TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	979 (38.8)	25 (1.0)	0	0	1,083 (44.4)	31 (1.3)	0	0
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	594 (23.5)	6 (0.2)	0	0	192 (7.9)	1 (<0.1)	0	0
Headaches	579 (22.9)	11 (0.4)	0	0	420 (17.2)	4 (0.2)	0	0
Fatigue	575 (22.9)	21 (0.8)	0	0	329 (13.5)	4 (0.2)	0	0
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SARS-CoV-2 test positive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hot flush	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alopecia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	368 (14.6)	16 (0.6)	0	0	135 (5.5)	3 (0.1)	0	0
Cough	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Leukopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lymphoedema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypomagnesaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SARS-CoV-2 test negative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Dyspepsia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma-glutamyl transferase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Breast pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Electrocardiogram QT prolonged	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vulvovaginal dryness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Influenza like illness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dry eye	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dry skin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Muscle spasms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Palpitations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal chest pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastroesophageal reflux disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood magnesium decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood alkaline phosphatase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Osteopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Osteoporosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rhinorrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vertigo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neck pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lacrimation increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mucosal inflammation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood bilirubin increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Joint stiffness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Procedural pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chest pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasal congestion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood lactate dehydrogenase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-cardiac chest pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Osteoarthritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neuropathy peripheral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axillary pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peripheral swelling	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Hypercalcaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spinal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal stiffness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: Preferred terms are sorted in descending frequency based on frequency in ribociclib plus AI arm.
MedDRA Version 27.0 has been used for reporting
Abbreviations: AE: adverse event; AI: aromatase inhibitor; TEAE: treatment emergent adverse event.
Source: Novartis Data on File (NATALEE Clinical Study Report April 2024 Data Cut: Table 4-6);[79] Fasching *et al.* (2024).[93]

B.2.9.3 Adverse events leading to discontinuation

At the April 2024 data cut, AEs leading to discontinuation of study treatment were reported more commonly in the ribociclib plus AI arm [redacted] compared with the AI arm [redacted]. The most commonly-reported AEs (in ≥10 patients) leading to study treatment drug discontinuation in the ribociclib plus AI arm were alanine aminotransferase increased [redacted], aspartate aminotransferase increased [redacted], arthralgia [redacted], fatigue [redacted], neutropenia [redacted], nausea [redacted], and asthenia [redacted]. The most commonly-reported AE leading to study treatment discontinuation in the AI arm was arthralgia [redacted]. Grade 3–5 AEs leading to study treatment discontinuation were reported in approximately [redacted] of patients in the ribociclib plus AI arm and in approximately [redacted] of patients in the AI arm.

Table 39: AEs leading to discontinuation irrespective of causality, by preferred term and maximum grade in NATALEE (≥ 0.2% for all grades in either arm) (April 2024 data cut) – safety set

	Ribociclib plus AI N=2,526				AI N=2,441			
Preferred term	**All Grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**All Grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
Number of patients with at least one TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Asthenia								
Blood creatinine increased								
Electrocardiogram QT prolonged								
Hepatotoxicity								
Blood magnesium decreased								
COVID-19								
Diarrhoea								
Headache								
Neutrophil count decreased								
Rash								
Hypomagnesaemia								
Pneumonitis								
Pulmonary embolism								
Alopecia								
Anxiety								
COVID-19 pneumonia								
Gamma-glutamyltransferase increased								
Hot flush								
Hypercalcaemia								
Hyperkalaemia								
Hypertransaminasaemia								
Papillary thyroid cancer								
Myalgia								

Footnotes: Preferred terms are sorted in descending frequency based on frequency in ribociclib plus AI arm.
MedDRA Version 25.1 has been used for reporting.
Abbreviations: AI: aromatase inhibitor; TEAE: treatment emergent adverse event.
Source: Novartis Data on File (NATALEE Clinical Study Report April 2024 Data Cut: Table 4-10).[79]

B.2.9.4 Adverse events of special interest

Table 40 presents the AESI recorded as of the April 2024 data cut. The overall pattern of AESI associated with the combination treatment of ribociclib plus AI was consistent with the known safety profile of both ribociclib and AI in the advanced or metastatic setting. AESI were more commonly reported in the ribociclib plus AI arm compared with the AI arm [redacted]. The most observed AESI (with incidences ≥20%) in the ribociclib plus AI arm were grouped events of neutropenia (62.8%), infections [redacted], hepatobiliary toxicity (26.7%), and leukopenia [redacted]. Grade 3 AESI were reported in [redacted] of patients in the ribociclib plus AI arm and [redacted] of patients in the AI arm, and grade 4 AESI were reported in [redacted] and [redacted] of patients, respectively. Grade 5 AESI were reported in [redacted] and [redacted] of patients in the ribociclib plus AI and AI arms, respectively (Table 36).

Table 40: AESIs by grouping irrespective of causality in NATALEE (April 2024 data cut) – safety set

	Ribociclib plus AI (N=2,526)				AI (N=2,441)			
MedDRA term	**All Grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**All Grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
Myelosuppression AESI								
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	1,587 (62.8)	[redacted]	[redacted]	[redacted]	111 (4.5)	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-myelosuppression AESI								
Hepatobiliary toxicity	675 (26.7)	173 (6.8)	45 (1.8)	0	279 (11.4)	41 (1.7)	1 (<0.1)	0
ILD pneumonitis	41 (1.6)	0	0	0	21 (0.9)	2 (0.1)	0	0
Infections	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QT interval prolongation	136 (5.4)	24 (1.0)	0	1 (<0.1)	38 (1.6)	17 (0.7)	0	0
Renal toxicity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reproductive toxicity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: AESI categories are presented in alphabetical order. AESIs may fall under more than one category but are only reported once per AESI category. MedDRA Version 27.0 has been used for reporting. AESI groupings per eCRS Version dated 04-May-2024.
Abbreviations: AESI: adverse event of special interest; AI: aromatase inhibitor; ILD: interstitial lung disease.
Source: Novartis Data on File (NATALEE Clinical Study Report April 2024 Data Cut: Table 4-12);[79] Fasching *et al.* (2024).[93]

B.2.9.5 Patient deaths

As of the April 2024 data cut, a total of [redacted] and [redacted] patients died during the study in the ribociclib plus AI and AI arms, respectively (Table 41). The main cause of deaths during the study, in both the ribociclib plus AI and AI treatment arms, was disease recurrence/progression [redacted]

[redacted] in the ribociclib plus AI arm and [redacted] in the AI arm died due to AE with fatal outcome. [redacted] in the ribociclib plus AI arm and [redacted] in the AI arm died due to reasons other than those listed in Table 41

Table 41: All deaths by primary reason for death and preferred term in NATALEE (April 2024 data cut) – safety set

Primary System Organ Class Primary Reason (Preferred Term)	Ribociclib plus AI N=2,526	AI N=2,441
Number of patients who died	[redacted]	[redacted]
Disease recurrence/progression	[redacted]	[redacted]
AE	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Acute myocardial infarction	[redacted]	[redacted]
Cardiac arrest	[redacted]	[redacted]
Cardiac failure congestive	[redacted]	[redacted]
Cardio-respiratory arrest	[redacted]	[redacted]
Cardiogenic shock	[redacted]	[redacted]
Cardiovascular insufficiency	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
Road traffic accident	[redacted]	[redacted]
Toxicity to various agents	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Brain oedema	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]
Other	[redacted]	[redacted]
Death	[redacted]	[redacted]
General physical health deterioration	[redacted]	[redacted]
Acute myeloid leukaemia	[redacted]	[redacted]

Sepsis	[redacted]	[redacted]

Footnotes: MedDRA Version 27.0 has been used for reporting.
Abbreviations: AE: adverse event; AI: aromatase inhibitor.
Source: Novartis Data on File (NATALEE Clinical Study Report April 2024 Data Cut: Table 4-8).[79]

B.2.10 Ongoing studies

The pivotal trial for ribociclib in this indication, NATALEE, is ongoing. Later data cuts from the NATALEE trial are planned for the second half of 2025, 2026 and 2027. It is therefore not anticipated that any additional data (beyond the April 2024 data cut presented within this submission) will become available during this appraisal.

ADAPTcycle is an ongoing trial comparing ribociclib plus AI to chemotherapy plus AI in patients with intermediate-risk HR+/HER2– EBC.[111] ADAPTcycle is not of relevance to this submission for several reasons. Specifically, the patient population in ADAPTcycle is not identical to NATALEE (although there may be overlap) as enrolment criteria is based on recurrence scoring from Oncotype DX, which was only used as an eligibility criteria for patients with node-negative Stage IIA HR+/HER2– EBC in NATALEE.[2] In addition, patients in ADAPTcycle can receive ribociclib plus AI in the neoadjuvant or adjuvant setting (as opposed to the adjuvant setting only in NATALEE), and the ribociclib treatment duration in ADAPTcycle is restricted to two years (compared with three years in NATALEE). Moreover, the comparator to ribociclib plus AI in ADAPTcycle is chemotherapy plus AI, which is not of relevance to this submission. Lastly, the first trial read out of ADAPTcycle will not be available until 2025.

B.2.11 Interpretation of clinical effectiveness and safety evidence

B.2.11.1 Principle findings from the clinical evidence base

In Population 1 (NATALEE ITT*)*, ribociclib plus AI was associated with statistically significant, clinically meaningful improvements in efficacy compared with AI, based on the NATALEE trial

At the April 2024 data cut (data cut-off: 29th April 2024, corresponding to median duration of follow-up of [redacted], and 603 iDFS events), NATALEE demonstrated statistically superior efficacy for ribociclib plus AI vs AI in Population 1 (NATALEE ITT).

At the April 2024 data cut (data cut-off: 29th April 2024) for Population 1 (NATALEE ITT), ribociclib plus AI statistically significantly reduced the risk of developing invasive disease by 28.5% compared with AI (HR: 0.715; 95% CI: 0.609, 0.840, one-sided stratified log-rank test p-value=0.0001), with a 4.9% absolute benefit in 4-year iDFS rates in favour of ribociclib plus AI (88.5% vs 83.6%). This result represents an improvement from the PA (July 2023), which estimated a 25.1% relative reduction in the risk of an iDFS event for ribociclib plus AI compared with AI. Additionally, consistency of iDFS improvement for ribociclib plus AI vs AI was evident across all subgroups assessed, including anatomic staging, menopausal status, and nodal involvement, demonstrating strong validity of the results across the broad study population.

The secondary endpoints, including RFS (at the PA [July 2023] and the April 2024 data cut), DDFS (at the PA [July 2023] and the April 2024 data cut) were consistent with, and supportive of, the primary endpoint iDFS results. At the April 2024 data cut, ribociclib plus AI [redacted] reduced the risk of developing recurrent disease by [redacted] compared with AI; similarly at the April 2024 data cut,

ribociclib plus AI was estimated to statistically significantly reduce the risk of distant recurrence by 28.5% (HR: 0.715; 95% CI: 0.604, 0.847, one-sided stratified log-rank test p-value<0.0001) and distant disease by 29.5% (HR: 0.705; 95% CI 0.589, 0.844, one-sided stratified log-rank test p-value<0.0001) compared with AI. Notably, these results represent an increased relative reduction since results from the PA (July 2023), which estimated a relative risk reduction of 27.5% and 25.1% for RFS and DDFS, respectively. Concordant results from these additional recurrence-based endpoints further confirm the broad-based efficacy of ribociclib plus AI in reducing the risk of disease recurrence both in terms of local/regional and distant recurrences in patients with EBC.

Establishing evidence for anticipated improvements in OS with ribociclib plus AI will require a prolonged follow-up, and OS data from NATALEE will not be fully mature during the timeframe for this evaluation. However, while the OS follow-up is still ongoing, OS results at the April 2024 data cut for Population 1 (NATALEE ITT) (HR: 0.827; 95% CI: 0.636, 1.074, one-sided stratified log-rank test=0.0766), indicate an early positive trend in favour of the ribociclib plus AI trial arm. Notably, the OS results at the April 2024 data cut improved from results at the PA (July 2023) (HR: 0.892; 95% CI: 0.661, 1.203; one-sided nominal p-value=[redacted]) leading to the potential for a continuing (improving) trend in OS at later data cuts. Such a hypothesis is supported by findings for ribociclib plus AI in the advanced or metastatic setting. For example, the MONALESSA-2 trial (comparing ribociclib plus AI to AI in the advanced or metastatic breast cancer setting) demonstrated that while data for OS were immature at the time of the primary and updated analyses, at the protocol-specified final analysis of OS (representing a median follow-up of 6.6 years), ribociclib plus AI showed a statistically significant OS benefit as compared with placebo plus AI (HR: 0.76; 95% CI: 0.63 to 0.93; two-sided p-value=0.008).[94] This therefore supports the hypothesis that the early OS benefit in favour of ribociclib plus AI (compared with AI) observed in the EBC-setting may continue to increase over time.[94]

In Population 2 (NATALEE node-positive high-risk), ribociclib plus AI was associated with statistically significant, clinically meaningful improvements in efficacy (as measured by iDFS) compared with AI, based on the NATALEE trial. In Population 3 (NATALEE node-negative high-risk), ribociclib plus AI was associated with a reduced risk of an iDFS event compared with AI, although this reduction was not statistically significant

At the April 2024 data cut of the NATALEE trial, the iDFS HR for ribociclib plus AI vs AI was 0.731 (95% CI: 0.617, 0.866) in Population 2 (NATALEE node-positive high-risk), representing a 26.9% relative reduction in the risk of an iDFS event, and was 0.666 (95% CI: 0.397, 1.118) in Population 3 (NATALEE node-negative high-risk), representing a 33.4% relative reduction in the risk of an iDFS event. Notably, the results across Population 2 (NATALEE node-positive high-risk) and Population 3 (NATALEE node-negative high-risk) were similar to the 28.5% relative reduction in the risk of an iDFS event observed across the FAS (Population 1 [NATALEE ITT]), at the April 2024 data cut. Taken together, the iDFS improvement for ribociclib plus AI vs AI was consistent across both subgroups by nodal status (Populations 2 and 3) and with the full population (Population 1 [NATALEE ITT]).

In Population 1 (NATALEE ITT), ribociclib plus AI was associated with a predictable and manageable safety profile, based on the NATALEE trial

Safety results from NATALEE for Population 1 (NATALEE ITT) at the April 2024 data cut demonstrate that a 400 mg starting dose of ribociclib plus AI has a predictable and manageable safety profile in the EBC setting. When compared with ribociclib in advanced or metastatic breast

cancer (MONALEESA-7),[112] no new safety signals or safety concerns were identified based on a thorough review of the safety data from NATALEE. Ribociclib-related AEs are well characterised from the advanced or metastatic breast cancer indication and are readily identifiable with routine laboratory tests or physical examination, are manageable with appropriate intervention (standard medical care and/or through the use of ribociclib dose reduction, temporary treatment interruption), and are reversible upon treatment adjustment. With the lower starting dose of 400 mg (compared with 600 mg in the advanced or metastatic breast cancer setting), a lower overall severity and incidence of toxicities was observed within NATALEE trial, specifically in terms of dose-dependent toxicities including QT interval prolongation and neutropenia.

The most common TEAEs (all grades, irrespective of causality) in the ribociclib plus AI arm of the NATALEE trial for Population 1 (NATALEE ITT) were [redacted], arthralgia (38.8%), and [redacted], which were consistent with the known AEs observed when the individual components of study treatment, ribociclib and AI, are administered separately. Grade ≥3 TEAEs observed in the ribociclib plus AI arm were consistent with the known safety profile of ribociclib, with most events recorded relating to the known risk of myelosuppression, occurring early during the course of treatment, and with their incidence not increasing over time. As might be expected, higher incidences of TEAEs leading to discontinuation of study treatment occurred in the ribociclib plus AI arm in comparison to the AI arm [redacted]. Finally, the ribociclib dose adjustment rate due to TEAEs was [redacted], and largely mandated by protocol guidance for dose adjustment.

At the April 2024 data cut of the NATALEE trial, the median follow-up was [redacted] and all patients had discontinued ribociclib; the level of follow-up completed in NATALEE thus far was adequate to detect any signals that were related to the safety profile of ribociclib, including those that were not dose dependent and/or rare events, and this is unlikely to change substantially with longer follow up.

Importantly, the clinical benefit observed in the NATALEE trial was not achieved at the detriment of patient wellbeing. Treatment with ribociclib plus AI compared with AI in Population 1 (NATALEE ITT) did not result in any notable deteriorations in HRQoL as measured using PROs at IA3 (January 2023). For both the physical functioning scores of the EORTC-QLQ-C30, and VAS scores of the EQ-5D-5L, there were no meaningful differences between the two treatment arms over time. All PRO scores in the ribociclib plus AI arm, upon treatment, remained within 0.5 standard deviations of their baseline scores. Overall, the treatment benefit associated with the addition of ribociclib to AI was observed without compromising patient HRQoL, as shown by the maintained PRO scores over time.

In the primary MAIC analysis conducted for Population 4 (node-positive high-risk eligible for abemaciclib), no statistically significant differences in treatment effect in terms of iDFS and OS were identified between ribociclib plus AI and abemaciclib plus ET

As ribociclib plus AI has not been directly compared in a head-to-head trial vs abemaciclib plus ET or vs ET in Population 4 (node-positive high-risk eligible for abemaciclib), an ITC was required to enable their comparison in this subgroup. The primary MAIC analysis in Population 4 (node-positive high-risk eligible for abemaciclib) demonstrated that across the two efficacy endpoints explored (iDFS and OS), there was no statistically significant difference in treatment effect between ribociclib plus AI and abemaciclib plus ET. Before matching, the unweighted comparison of results slightly favoured abemaciclib plus ET for iDFS and ribociclib plus AI for OS, although the differences were not statistically significant. After matching (using the MAIC

methodology), all outcomes directionally shifted towards ribociclib plus AI (iDFS [redacted] and OS [redacted]). The results from the additional sensitivity analysis (adjusting for an alternative, reduced set of variables), demonstrated consistent findings with the primary MAIC analysis results.

Comparisons of grade 3 or higher TEAEs with incidence of at least 5% demonstrated statistically significantly lower odds of occurrence in patients treated with ribociclib plus AI vs abemaciclib plus ET for diarrhoea (a key symptomatic AE), leukopenia, and lymphopenia, before and after MAIC weighting in Population 4 (node-positive high-risk eligible for abemaciclib). However, ribociclib plus AI demonstrated statistically significantly greater odds than abemaciclib plus ET in the incidence of increased alanine aminotransferase and neutropenia.

In the primary MAIC analysis conducted for Population 4 (node-positive high-risk eligible for abemaciclib), statistically significant improvements in iDFS, although not for OS, were identified between ribociclib plus AI and ET

Finally, before and after matching, ribociclib plus AI was associated with statistically significantly improved iDFS vs ET in Population 4 (node-positive high-risk eligible for abemaciclib; before matching [redacted]; after matching [redacted]. The unmatched and matched comparison of results for OS also slightly favoured ribociclib plus AI vs ET, although the differences were not statistically significant.

B.2.11.2 Strengths and limitations of the clinical evidence base

Strengths

The clinical evidence base presented in this submission was identified from a clinical SLR that was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and PRISMA guidelines.[113] NATALEE was the only relevant clinical trial identified by the clinical SLR for ribociclib plus AI in this indication, which comprises a global, multicentre, Phase III randomised controlled trial. As described in Section B.1.1.1, whilst the NATALEE trial was open label, the randomised, stratified, multicentre design of NATALEE minimised allocation bias, balancing key prognostic factors in the assignment of treatments. Using the York CRD checklist,[114] NATALEE was considered a well conducted study at low risk of bias.

The NATALEE trial provides key evidence of the clinically meaningful benefit of ribociclib plus AI in a broad population of patients with HR+/HER2– EBC at high risk of recurrence, including patients with node-negative disease (representing 22.1% of all HR+/HER2– EBC patients at high risk of recurrence), and patients with N1 disease without additional specific anatomical risk factors (representing 33.0% of all HR+/HER2– EBC patients at high risk of recurrence), who are currently ineligible to access other CKD4/6 inhibitors such as abemaciclib.[7]

The endpoints investigated in the NATALEE trial are clinically relevant and of importance to patients with EBC at high risk of recurrence. The primary endpoint, iDFS (defined as per the STEEP criteria),[90] has been frequently used in published adjuvant EBC therapy studies to date.[77, 115-117] Additionally, iDFS events in NATALEE were assessed by clinical/radiological assessments confirmed by histological/cytological assessments (where appropriate), supporting the validity and objectiveness of the underlying recurrence assessment for iDFS.

Finally, NATALEE enrolled 83 patients from 11 sites across the UK. The evidence from NATALEE is considered generalisable to the UK, with clinical experts confirming the baseline

characteristics and treatment regimens included in the trial aligned with UK clinical practice (see Appendix Q.2).

Limitations

The open-label nature of NATALEE represents a necessary limitation of the trial design, as the toxicities and laboratory abnormalities (particularly neutropenia) associated with ribociclib were not likely to be compatible with maintaining a blinded study. However, steps were taken to minimise bias during the analysis of the trial data. Firstly, the study team was blinded to aggregate reports by treatment arm until the time of final iDFS analysis (or until after interim iDFS analysis if futility or superiority was declared). For iDFS, all unblinded results were not communicated to the Novartis clinical team or to any party involved in the study conduct (apart from the independent statistician and data monitoring committee members). Additionally, iDFS events were based on both clinical/radiological assessment and histological/cytological assessment as highlighted above, which are all objective measures of assessment. These steps ensured that the results of the study were not affected by the open-label design.

In addition, anastrozole and letrozole were the only therapies included in the comparator arm of the NATALEE trial, however in UK clinical practice, ET constitutes a basket of therapies including exemestane and tamoxifen. As discussed in Section B.1.3.4, there is a wealth of evidence demonstrating that AIs are more effective than tamoxifen at reducing disease recurrence in EBC (see Appendix M.1). The efficacy of the NATALEE AI arm was therefore adjusted in the economic analyses to account for a proportion of patients receiving tamoxifen and reflect the overall efficacy of ET (see Section B.3.3.3).

Additional limitations arise from uncertainties in the MAIC. Firstly, despite steps being taken to ascertain and adjust for important differences between the NATALEE-selected and Cohort 1 monarchE populations, some additional differences may have been unobserved or unreported, and therefore remained unadjusted for. Secondly, due to differences in eligibility criteria between the monarchE and NATALEE trials, the NATALEE population included in the MAIC was considerably smaller than the original NATALEE sample size for each treatment arm. This reduced the patient pool and a potential break in randomisation from the original NATALEE ITT population may have biased the comparison of outcomes; however, given the ESS included a substantial number of patients, the reliability of results is not anticipated to have been affected. Lastly, although unlikely to bias the findings, the Kaplan-Meier curves from monarchE trial were based on reconstructed IPD, and it was not possible to exactly match the Kaplan-Meier curves used in the analyses to those reported in monarchE publications.

B.2.11.3 Overall conclusions

The clinical effectiveness evidence presented above highlights that ribociclib plus AI addresses the clear unmet need in reducing the risk of recurrence for patients in Population 1 (NATALEE ITT).

Ribociclib plus AI [redacted] improved iDFS, RFS, and DDFS compared with AI in Population 1 (NATALEE ITT), and was shown to have a well-established and tolerable safety profile. Notably, the iDFS improvement for ribociclib plus AI vs AI was generally consistent across the subgroups of patients based on menopausal status, anatomic stage, prior chemotherapy, geographic region, Ki-67 status, nodal status and prior ET, including across Population 2 (NATALEE node-positive high-risk) and Population 3 (NATALEE node-negative

high-risk). In Population 4 (node-positive high-risk eligible for abemaciclib), the MAIC analyses showed no statistically significant difference in terms of treatment effect (as measured by iDFS and OS) between ribociclib plus AI and abemaciclib plus ET, and statistically significant improvements in iDFS, although not OS, between ribociclib plus AI and ET, demonstrating that ribociclib plus AI can provide an alternative treatment option in this population.

B.3 Cost effectiveness

Summary

- A cost-utility model was developed to assess the cost-effectiveness of ribociclib plus AI vs the relevant comparators for this submission in patients with HR+/HER2– EBC at high risk of recurrence.
- The base case economic analysis compared ribociclib plus AI vs ET in Population 1 (NATALEE ITT) i.e., patients with HR+/HER2– EBC at high risk of recurrence (see Section B.1.1 for full definition). In addition, three subgroup economic analyses were conducted in Populations 2–4 (see Section B.1.1 for full definitions).
- The cost-utility model was developed in line with the NICE reference case and from an NHS and Personal Social Services (PSS) perspective. The model structure adopted a semi-Markov approach in line with previous EBC models in this population, with a lifetime time horizon and a 28-day cycle length.
- The model consisted of a cohort state-transition model with six health states: iDFS, non-metastatic recurrence (NMR), second primary malignancy (SPM), remission, distant recurrence (DR), and death. The death, SPM and DR health states were modelled as absorbing health states. The DR health state was divided into two substates; ET-resistant and ET-sensitive. Transition into these substates was dependent on how long it took patients to experience disease recurrence after completing adjuvant ET.
- For the economic analyses in Population 1 (NATALEE ITT) and Populations 2 and 3 (NATALEE node-positive high-risk and node-negative high-risk), clinical efficacy inputs were derived directly from the NATALEE trial (April 2024 data cut).[92] The AI arm of the NATALEE trial was used to inform the efficacy of ET (with an adjustment to reflect the efficacy of tamoxifen), and iDFS and time to treatment discontinuation (TTD) data for ribociclib plus AI and AI from the NATALEE trial were used to parameterise health state transitions for the ribociclib plus AI and ET arms of the model, respectively.
- For the economic analysis in Population 4 (node-positive high-risk eligible for abemaciclib), clinical efficacy inputs for ribociclib plus AI, abemaciclib plus ET and ET were derived from a MAIC conducted between the relevant NATALEE trial population and Cohort 1 of monarchE,[107] the pivotal trial for abemaciclib plus ET in this subgroup (see Section B.2.8).
- Health state utility values across all four economic analyses were derived from EQ-5D-5L data collected in the ITT population of NATALEE and mapped to the EQ-5D-3L as per the NICE reference case.
- Cost categories included in the model were drug acquisition costs (at the PAS price for ribociclib and alpelisib, and the list price for all other therapies), drug administration costs, AE costs, monitoring and follow-up costs, subsequent treatment costs and end-of-life costs.

Results of the base case economic analysis of ribociclib plus AI vs ET in Population 1 (NATALEE ITT)

- In the probabilistic base case economic analysis for Population 1 (NATALEE ITT), ribociclib plus AI was associated with [redacted] more quality-adjusted life years (QALYs) and

reduced total costs of [redacted] vs ET, resulting in ribociclib plus AI dominating ET in this population. The probability of ribociclib plus AI being cost-effective vs ET was [redacted] and [redacted] at the £20,000 and £30,000 willingness-to-pay (WTP) thresholds, respectively.

- Deterministic sensitivity analysis (DSA) revealed the most influential drivers of the analysis were the PFS HRs applied for capecitabine in the ET-sensitive health state, the PFS HRs applied for abemaciclib plus fulvestrant in the ET-resistant health state, and the efficacy discount rate
- Deterministic scenario analyses were conducted to assess the robustness of the base case assumptions, and across the majority of scenario analyses, ribociclib plus AI remained dominant vs ET in Population 1 (NATALEE ITT).

Results of the subgroup economic analyses of ribociclib plus AI vs ET in Population 2 (NATALEE node-positive high-risk) and Population 3 (NATALEE node-negative high-risk)

- In the probabilistic subgroup economic analysis in Population 2 (NATALEE node-positive high-risk) and Population 3 (NATALEE node-negative high-risk), ribociclib plus AI was associated with [redacted] and [redacted] more QALYs and reduced total costs of [redacted] and [redacted] vs ET, respectively, resulting in ribociclib plus AI dominating ET in both populations.
- Deterministic scenario analyses were conducted to assess the robustness of the analysis assumptions, and across the majority of scenario analyses, ribociclib plus AI remained dominant vs ET in Population 2 (NATALEE node-positive high-risk) and Population 3 (NATALEE node-negative high-risk).

Results of the subgroup economic analyses of ribociclib plus AI vs abemaciclib plus ET and ET in Population 4 (node-positive high-risk eligible for abemaciclib)

- In the probabilistic base case analysis in Population 4 (node-positive high-risk eligible for abemaciclib), ribociclib plus AI (with the PAS for ribociclib) was associated with [redacted] more QALYs and decreased total costs of [redacted] in comparison to ET, resulting in ribociclib plus AI dominating ET in this population. Additionally, ribociclib plus AI (with the PAS for ribociclib) was associated with [redacted] more QALYs and decreased total costs of [redacted] in comparison to abemaciclib plus ET, resulting in ribociclib plus AI dominating abemaciclib plus ET in this population.
- Deterministic scenario analyses were conducted to assess the robustness of the analysis assumptions, and across all scenario analyses, the results were in line with the base case subgroup economic analysis results in Population 4 (node-positive high-risk eligible for abemaciclib).

Overall summary

- The results across the economic analyses in all four populations indicate that ribociclib plus AI dominates all comparators, thereby representing a cost-effective use of NHS resources and a promising new therapy for patients with HR+/HER2– EBC at high risk of recurrence.

B.3.1 Published cost-effectiveness studies

Economic SLRs were conducted in April 2023, and subsequently updated in October 2023 and July 2024 to identify relevant economic evaluations, utilities studies and cost and resource use studies conducted in patients with HR+/HER2– EBC.

Full details of the methodology and results of the economic SLRs, including the search strategy and the study selection process, are presented in Appendices G, H and I for the economic evaluations, utility studies, and cost and resource use studies SLRs, respectively.

Across both the original SLR of economic evaluations and the two SLR updates, a total of 16 studies (reported in 22 records) were included. Of these, 11 studies were published economic evaluations and 5 were published HTA reports. An overview of these 16 studies is provided in Table 42. No studies evaluating the cost-effectiveness of ribociclib plus AI in patients with HR+/HER2– EBC were identified.

In terms of model structure, 15 of the 16 studies employed a cohort-state transition model;[6, 118-131] the remaining study (a published economic evaluation) did not provide information regarding the economic model, and it was conducted alongside a clinical trial.[132] In terms of the health states employed, ten of the 11 published economic evaluations provided information regarding the modelled health states.[118-126, 131] Most of these included five health states within their economic models, namely iDFS, NMR, MR, remission and death. The five HTA reports all also used the same five health states. Notably, only one of the economic evaluations was conducted from a UK NHS and PSS perspective (TA810).[6]

An overview of the economic evaluations identified in the SLR is provided in Table 42.

Table 42: Summary of models across the economic evaluations identified in the SLR

Study names	Country	Type of evaluation	Model perspective	Model design	Health states	Cycle length	Time horizon	Discounting (costs)	Currency	Cost year
Published economic evaluations										
Jongbloed *et al.* (2023)[118]	Netherlands	CEA	Societal	Cohort state-transition model	• Recurrence free • Recurrent disease • Death	3 months	Lifetime	4.0%	Euro (€)	2021
Talwar *et al.* (2023)[119]	US	CEA	Third party payer	Cohort state-transition model	• Progression-free disease • Progressive disease • Death due to disease • Death due to other causes	NR	Lifetime	NR	USD ($)	NR
Chang *et al.* (2022)[120]	US	CEA	Payer	Cohort state-transition model	• EBC progression-free • Progressed disease • MBC progression-free • MBC-progression • Death	6 months	10 years	3.0%		2022
Galactionova *et al.* (2022)[132]	Global (Germany, Spain, US, France, Australia, South Korea, Ireland, Japan, Austria, and UK)	CEA	German statutory health insurance	NR	NR	NR	Within-trial horizon with a maximum follow up of 6 years	3.0%	Euro (€)	2020

Study names	Country	Type of evaluation	Model perspective	Model design	Health states	Cycle length	Time horizon	Discounting (costs)	Currency	Cost year
Davie *et al.* (2023)[121]	Spain	CUA	Spanish healthcare	Cohort state-transition model	• iDFS • NMR • Remission • Metastatic recurrence • Death	28 days	Lifetime	3.0%	Euro (€)	2021 or latest available data
Davie *et al.* (2023)[122]	Italy	CUA	Italian healthcare system	Cohort state-transition model	• iDFS • NMR • Remission • Metastatic recurrence • Death	28 days	30 years	3.0%	Euro (€)	2021
Fenix-Caballero *et al.* (2024)[131]	Spain	CUA	Spanish healthcare system	Cohort state-transition model	• DFS • Local recurrence • Distal recurrence • Death	1 month	30 years	3.0%	Euro (€)	2022
Zhong *et al.* (2024)[123]	China	CEA	Chinese healthcare system	Cohort state-transition model	• DFS • Contralateral tumour • Locoregional recurrence • Distant metastasis • Second cancer • Death	1 year	25 years	5.0%	USD ($)	2021
Fariman *et al.* (2024)[124]	US	CEA	US societal	Cohort state-transition model	• Recurrence free • Recurrent disease • Thromboembolism and endometrial cancer • Death	NR	10 years	3.0%	USD ($)	2023

Study names	Country	Type of evaluation	Model perspective	Model design	Health states	Cycle length	Time horizon	Discounting (costs)	Currency	Cost year
Wei *et al.* (2023)[125]	China	CEA	Chinese healthcare system	Cohort state-transition model	• iDFS • NMR • Remission • Metastatic recurrence • Death	1 month	Lifetime	5.0%	USD ($)	2023
Sra *et al.* (2024)[126]	India	CEA	Indian payer	Cohort state-transition model	• DFS • Locoregional recurrence • Metastasis • All-cause mortality • Disease mortality	1 year	Lifetime (49 years)	3.0%	INR (₹) and USD ($)	2023
HTA report economic evaluations										
NICE TA810 (2022)[6]	UK	CEA, CUA	National Health Service (NHS) and Personal Social Services (PSS)	Cohort state-transition model	• iDFS • NMR • Remission • Metastatic recurrence • Death	28 days	Lifetime	3.5%	Pound (£)	2019/2020
SMC (2022)[127]	Scotland	CUA	NR	Cohort state-transition model		28 days	49 years	NR		NR
PBAC (2022)[128]	Australia	CUA	NR	Cohort state-transition model		28 days	40 years	NR	$	NR
CDA-AMC (2022)[129]	Canada	CUA	Canadian publicly funded	Cohort state-		28 days	Lifetime (49 years)	1.5%	$	NR

Study names	Country	Type of evaluation	Model perspective	Model design	Health states	Cycle length	Time horizon	Discounting (costs)	Currency	Cost year
			health care payer	transition model						
NCPE 2023 (2023)[130]	Ireland	CUA	NR	Cohort state-transition model		NR	Lifetime	4.0%	Euro (€)	NR

Abbreviations: CDA-AME: Canada's Drug Agency; CEA: cost-effectiveness analysis; CUA: cost-utility analysis; DFS: disease-free recurrence; EBC: early breast cancer; iDFS: invasive disease-free survival; MBC: metastatic breast cancer; NCPE: National Centre for Pharmacoeconomics; NICE: National Institute for Health and Care Excellence; NMA: non-metastatic recurrence; NR: not reported; PBAC: Pharmaceutical Benefits Advisory Committee; SMC: Scottish Medicines Consortium; UK: United Kingdom; US: United States; USD: US Dollar.

B.3.2 Economic analysis

Since the economic SLR did not identify any economic evaluations assessing the cost-effectiveness of ribociclib plus AI vs the relevant comparators in patients with HR+/HER2– EBC at high risk of recurrence, a *de novo* cost-utility model for ribociclib plus AI vs ET was developed for this submission, as described in the following sections.

Economic analyses have been conducted in four populations for this submission. Full details of the definitions of these populations are described below.

B.3.2.1 Patient population

Base case analysis

Population 1 (NATALEE ITT)

This population is defined as adult (i.e., aged at least 18 years) men and women of known menopausal status receiving adjuvant treatment for HR+/HER2– EBC at high risk of recurrence. High risk of recurrence in this submission is defined in line with the eligibility criteria of the NATALEE trial (see Section B.1.1), as adult patients with HR+/HER2– EBC that is:[2]

- Anatomical Stage IIA
  - N0 with either:
    - Grade 3, or
    - Grade 2, with any of the following criteria: Ki67 ≥20%, Oncotype DX, Breast Recurrence Score ≥26, Prosigna/PAM50 categorised as high risk, MammaPrint categorised as high risk or EndoPredict EPclin Risk Score categorised as high risk
  - N1
- Anatomical Stage IIB
  - N0 or N1
- Anatomical Stage III
  - N0, N1, N2 or N3

The relevant comparator to ribociclib plus AI in Population 1 (NATALEE ITT) is ET.

Subgroup analyses

Population 2 (NATALEE node-positive high-risk)

The patient population considered within this subgroup analysis is defined per the NATALEE trial eligibility criteria as patients with HR+/HER2– EBC that is:[2]

- Anatomical Stage IIA
  - N1
- Anatomical Stage IIB
  - N1
- Anatomical Stage III

- N1, N2 or N3

The comparator considered in this population is ET.

Population 3 (NATALEE node-negative high-risk)

The patient population considered within this subgroup analysis is defined per the NATALEE trial eligibility criteria as patients with HR+/HER2– EBC that is:[2]

- Anatomical Stage IIA
  - N0 with either:
    - Grade 3, or
    - Grade 2, with any of the following criteria: Ki67 ≥20%, Oncotype DX, Breast Recurrence Score ≥26, Prosigna/PAM50 categorised as high risk, MammaPrint categorised as high risk or EndoPredict EPclin Risk Score categorised as high risk
- Anatomical Stage IIB
  - N0
- Anatomical Stage III
  - N0

The comparator considered in this population is ET.

Population 4 (node-positive high-risk eligible for abemaciclib)

The patient population considered within this subgroup analysis is defined per the population evaluated in NICE TA810,[6] which is node-positive HR+/HER2–EBC with pathological tumour involvement in:

- ≥4 ALNs, or
- 1–3 ALNs with either:
  - Grade 3 disease or
  - primary tumour size ≥5 cm

The comparators considered in this population are abemaciclib plus ET and ET.

B.3.2.2 Model structure

The model structure of the cost-utility analysis was a non-homogeneous semi-Markov cohort state-transition model with six health states defined by disease recurrence and death. This model structure was chosen for a number of reasons:

- All 16 of the economic evaluations identified in the SLR of economic evaluations detailed in Section B.3.1 were cohort state-transition models with health states defined by disease recurrence and death.[6, 118-132] The main reason for this is that in EBC, there are inherently insufficient long term follow-up data to populate a partitioned survival model (PSM). As such, a semi-Markov cohort state-transition model takes into account the data maturity and availability for the relevant intervention and comparators. It also captures the natural

progression of patients with HR+/HER2– EBC and the disease pathway from EBC to advanced or metastatic breast cancer.

- The model structure adopted in the only NICE evaluation to date in patients with EBC at high risk of recurrence (TA810 for abemaciclib plus ET)[6] was also a semi-Markov cohort state-transition model with five health states defined by disease recurrence and death. This model was deemed by the EAG to capture all relevant health states and therefore represents a previously reviewed and validated approach to modelling this indication
- Finally, feedback from clinical experts at an advisory board held by the Company in September 2024 agreed that the proposed model structure reflects the natural history of patients with HR+/HER2– EBC (see Appendix Q.3).

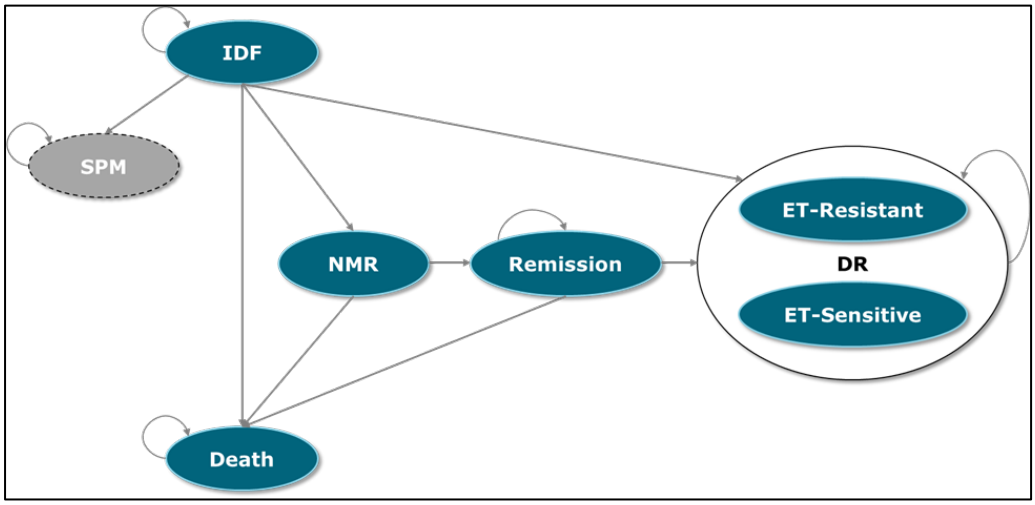
The term 'non-homogeneous' refers to a model that includes time-dependent transition matrices which are required when age-specific mortality rates are used. A semi-Markov model allows the inclusion of tunnel states with transition probabilities based on the time since entering a health state, which may be required for health states wherein the probability of transition out of the state increases or decreases over time since entry into the health state.

The six health states included in the model were defined based on disease-free status, type of recurrence (i.e., non-metastatic or distant), and death:

- Invasive disease-free (IDF) (akin to iDFS)
- Second primary malignancy (SPM)
- Non-metastatic recurrence (NMR)
- Remission
- Distant recurrence (DR)
- Death

A simplified schematic depicting the model structure is shown in Figure 29.

Figure 29: Simplified schematic of the model structure used in the cost-utility analyses



Abbreviations: DR: distant recurrence; ET: endocrine therapy; IDF: invasive disease-free; NMR: non-metastatic recurrence; SPM: second primary malignancy.

Model health states

iDFS health state

Patients are assumed to enter the model in the IDF (termed iDFS hereafter) health state. In each model cycle, patients in the iDFS state can either, a) remain in that health state, b) experience NMR (i.e., locoregional recurrence, contralateral recurrence) or SPM and transition to the NMR or SPM health states respectively, c) experience DR and transition to the DR state, or d) die.

The model does not include explicit health states for on- and off-treatment while in the iDFS health state but has the facility to partition patients remaining in this health state into on- and off-treatment based on the relevant time to treatment discontinuation (TTD) curve. The model also considers maximum treatment durations for all treatments, where patients remaining in iDFS after a pre-specified duration were assumed to no longer be receiving treatment (see Section B.3.5.1).

NMR and remission health states

Patients in the NMR health state either remain in that health state at the end of each model cycle or die. Patients who remain in the NMR state for 12 months transition to the remission health state. Those who enter the remission health state either, a) remain in that health state, b) experience DR or c) die. Patients who experience DR transit to the DR state. Patients who die transit to the death state. The NMR and remission health states include enough tunnel states to permit the probabilities of further progression and death to vary based on the length of time spent within the health state.

DR health state

Patients experiencing DR enter one of two substates, which were modelled as absorbing health states and stratified by the timing of recurrence. Those with a DR ≤12 months following completion of the ET component of each treatment arm were assumed to enter the ET-resistant substate, while those with a DR >12 months after completing their ET were assumed to enter the ET-sensitive substate. Across all four economic analyses, the use of this 12-month cut-off was based on the assumption that ET-sensitive advanced or metastatic disease would be defined as a first recurrence at least 72 months after starting adjuvant treatment, given than adjuvant ET is expected to typically be given for a maximum of ~60 months (~5 years). For patients discontinuing ET prior to 60 months (e.g. due to toxicity), the same 72-month rule applied, as per the approach used to inform decision making in TA810.[6] Furthermore, it was assumed that any patients considered ET-resistant at first recurrence (i.e., those experiencing a non-metastatic recurrence <72 months from the start of ET treatment), could not later be considered ET-sensitive. Feedback from UK clinical experts indicated that treatment with ET may continue beyond 5 years and could be given for up to 10 years in some patients (see Appendix Q.2). As such, scenario analyses were conducted whereby the maximum treatment duration of ET (and therefore the ET-sensitive threshold definition) was set to 7 years, and 10 years, to explore the impact of this assumption.

The DR substates were modelled using a PSM framework based on progression-free survival (PFS), OS and TTD curves for subsequent therapies received in the ET-sensitive and ET-resistant health states, respectively. Given the availability to Novartis of PFS, OS and TTD IPD for ribociclib when used in the advanced or metastatic setting, PFS, OS and TTD curves for ribociclib from MONALEESA-2 (for the ET-sensitive substate) and MONALEESA-3 (for the ET-

resistant substate) were used in the PSM framework and extrapolated to derive undiscounted life years (LYs) accrued in the DR health state; health-state utility values were applied to derive QALYs. HRs for other subsequent treatments were then applied to the MONALEESA-2 and MONALEESA-3 PFS, OS and TTD curves, based on data from the literature, identified via a TLR (see Appendix M.2).[87, 133]

Costs considered within the DR substate PSM framework included drug acquisition and administration costs of subsequent therapies (based on the TTD curves), follow-up and monitoring costs, post-progression treatment costs (implemented as a fixed monthly cost), and end-of-life costs. The total LYs, QALYs and costs outputted from the PSM framework were then weighted by the treatment mix in the ET-sensitive and ET-resistant substates and applied (with discounting) to patients entering the DR health state. Full details of the DR health state PSM approach are presented in Appendix S.

The approach to modelling the DR health state using a PSM framework allows for the costs and QALYs associated with this health state to be modelled more granularly and therefore more transparently, given the availability of clinical data from this setting from the MONALEESA-2 and MONALEESA-3 trials.[87, 133] A more simplistic lump sum approach using total costs and QALYs from previously-conducted economic evaluations to NICE was not possible as: a PSM model was not previously submitted to NICE in the ET-sensitive indication for ribociclib plus AI (MONALEESA-2). In addition, the PSM framework allowed for the most mature data with the longest follow-up available from MONALEESA-2 and MONALEESA-3 to be used. Finally, this approach also allows for the adjustment of PAS discounts for subsequent therapies received in the DR health state.

SPM and death health states

Both the SPM and death health states were modelled as absorbing health states. To maintain a simple model structure, the full pathway following a SPM was not modelled. Instead, patients who develop a SPM were assumed to incur a one-off cost of diagnosis and then leave the model. This approach was in line with the CEM that was used to inform decision making in TA810,[6] and was further validated by clinical experts at a recent advisory board (September 2024) who agreed that the whole model structure was reasonable (see Appendix Q.3).

A summary of the assumptions and justifications adopted for each health state in the model is provided in Section B.3.9.

Summary of model features

A 28-day cycle length was used in the model, as this was deemed sufficient to accurately capture relevant differences in clinical and cost outcomes between ribociclib plus AI and the relevant comparators. A half-cycle correction was applied to account for events not occurring at the beginning or end of every cycle. In line with the NICE reference case, a 3.5% discount rate was applied to both cost and effects.

The analysis was undertaken from a UK NHS and PSS perspective. In line with the NICE reference case, a lifetime time horizon was adopted to capture all relevant differences in clinical and cost outcomes between ribociclib plus AI and the relevant comparators. The lifetime time horizon corresponded to 50 years, based on the mean age in the NATALEE trial ITT population.

The key features of the economic analysis are outlined in Table 43, alongside the key features of

the economic model submitted in the NICE appraisal of abemaciclib (TA810).[6]

Table 43: Features of the economic analysis

	Previous NICE evaluations	Current evaluation	
Factor	**TA810[6]**	**Chosen values**	**Justification**
Model design	Semi-Markov cohort state-transition model	Semi-Markov model cohort state-transition model	In EBC there are inherently insufficient long term follow-up data to populate a PSM. In line with the previous NICE appraisal for abemaciclib in HR+/HER2– EBC (NICE TA810),[6] numerous published models in this indication (see Table 42) and validation from UK clinical experts (see Appendix Q.3), a semi-Markov model structure was considered appropriate.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	50 years (lifetime)	In line with the NICE reference case as sufficient to capture all meaningful differences in the technologies compared.
Perspective	UK NHS and PSS	UK NHS and PSS	In line with the NICE reference case.
Cycle length	28 days	28 days	A 28-day cycle length was deemed sufficient to accurately capture relevant differences in clinical and cost outcomes between ribociclib plus AI and the relevant comparators
Annual discount rate	3.5%	3.5%	In line with the NICE reference case.
Source of utilities	• monarchE for iDFS utility • Published utility values for post-iDFS health states • Committee-preferred utility values from TA725 and TA563 for metastatic health states	• iDFS (on and off treatment) – NATALEE data (April 2024 data cut) • NMR – NATALEE data (April 2024 data cut) • Remission utility assumed equal to iDFS per TA810[6] • PFS in DR health state - NATALEE data (April 2024 data cut) • PPS in DR	EQ-5D-5L utility data collected from the NATALEE trial were used where possible, and mapped to the EQ-5D-3L, in line with the NICE reference case. Where utility values were derived from the literature, NICE-Committee preferred utility values from previous NICE evaluations were used where possible.

		health state - relative decreases between PFS and PPS utilities as observed in MONALEESA-3 and MONALEESA-2 were used for the ET-resistant and ET-sensitive PPS states, respectively	
Treatment waning	Treatment waning effect applied for abemaciclib plus ET from 8 years to the point at which the iDFS event rate was equal to general population mortality	Treatment waning effect applied for ribociclib plus AI (all four populations) and for abemaciclib plus ET (Population 4) from 8 years to the point at which the iDFS event rate equals general population mortality	Based on the results of the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial,[134] which showed a 'carryover benefit' of a constant treatment effect lasting up to 8 years (see Section B.3.3.4 for full details of the treatment waning assumptions).
Source of costs and resource use	• National Schedule of NHS Costs 2019/20 • PSSRU 2020 • eMIT	• National Schedule of NHS Costs 2022/23 • eMIT • BNF	In line with the NICE reference case.
Health effects measure	QALYs	QALYs	In line with the NICE reference case.

Abbreviations: BNF: British National Formulary; EBC: early breast cancer; eMIT: electronic market information tool; iDFS: invasive disease-free survival; NHS: National Health Service; NICE: National Institute for Clinical Excellence; PSM: partitioned survival model; PSS: Personal Social Services; PSSRU: Personal Social Services Research Unit; TA: technology appraisal; UK: United Kingdom; QALYs: quality-adjusted life years.

B.3.2.3 Intervention technology and comparators

Intervention

Ribociclib plus AI

The intervention considered in all four economic analyses is ribociclib plus AI, modelled in line with the anticipated licensed dosing regimen in this indication and the dosing regimen received in the NATALEE trial, i.e., 400 mg (two 200 mg film-coated tablets) administered orally once daily for 21 consecutive days followed by seven days off treatment.[1, 2] Treatment duration with ribociclib was capped at 3 years, as per the maximum duration of treatment in the NATALEE trial and the anticipated ribociclib SmPC in this indication.[1, 2] Full details of the dosing regimens and drug acquisition costs for ribociclib plus AI are presented in Section B.3.5.1.

As there are a number of AI therapies that can be given in combination with ribociclib, AI was

modelled as a basket of AI therapies, which included anastrozole, letrozole and exemestane, in addition to the add-on therapies: gonadotropin hormone-releasing hormone (GnRH) goserelin, and the bisphosphonate zoledronic acid. The treatment mix of these AI therapies in the four economic analyses was based on the ribociclib plus AI arm of NATALEE and adjusted based on feedback from UK clinical experts collected at an advisory board held by the Company in September 2024 (see Appendix Q.3).

Full details of the treatment mix and the derivations of the proportion of patients assumed to receive each therapy within AI for each of the four economic analyses is presented in Section B.3.5.1.

Comparators

Population 1 (NATALEE ITT), Population 2 (NATALEE node-positive high-risk) and Population 3 (NATALEE node-negative high-risk)

The comparator in Populations 1–3 is ET.

ET was modelled as a basket of ETs, including letrozole, anastrozole, exemestane and tamoxifen, in addition to the add-on therapies goserelin and zoledronic acid. The treatment mix was based on the AI arm of NATALEE (with the addition of exemestane and tamoxifen) and adjusted based on feedback from UK clinical experts collected at an advisory board held by the Company in September 2024 (see Appendix Q.3). Full details of the treatment mix and the derivations of the proportion of patients assumed to receive each therapy within ET for Populations 1–3 is presented in Section B.3.5.1.

Population 4 (node-positive high-risk eligible for abemaciclib)

The comparators in Population 4 (node-positive high-risk eligible for abemaciclib) are abemaciclib plus ET and ET.

Abemaciclib was modelled in line with the licensed dosing regimen in this indication and the dosing regimen received in the monarchE trial.[77, 135] Treatment duration with abemaciclib was capped at 2 years, as per the maximum duration of treatment in the monarchE trial and the abemaciclib SmPC.[77, 135]

ET, both in combination with abemaciclib and alone, was modelled as per Populations 1–3. Full details are presented in Section B.3.5.1.

B.3.3 Clinical parameters and variables

B.3.3.1 Baseline characteristics

The baseline characteristics informing all four economic analyses were derived from the NATALEE trial, based on data from the respective populations, and are presented in Table 44.

The mean age of each population and the proportion of females in the trial were used to adjust for general population mortality. The mean BSA and weight were used to derive daily dosages for certain treatments used in the DR health states (see Section B.3.5.2).

Table 44: Summary of baseline characteristics used in the economic analyses

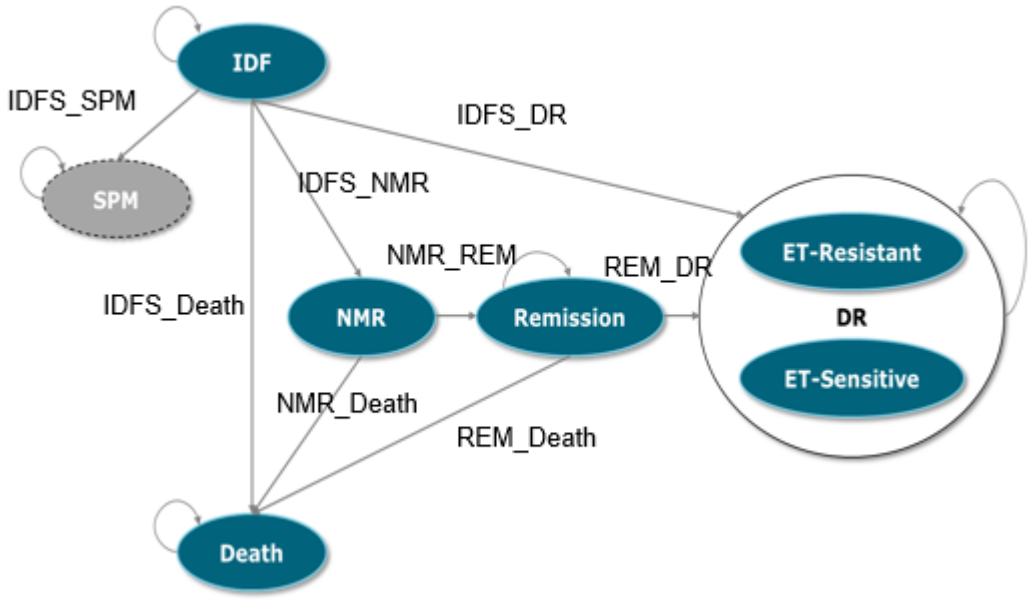
Variable	Population 1 (NATALEE ITT)	Population 2 (NATALEE node-positive high-risk)	Population 3 (NATALEE node-negative high-risk)	Population 4 (node-positive high-risk eligible for abemaciclib)
Mean age (years)	[redacted]	[redacted]	[redacted]	[redacted]
Proportion Female	99.60%	[redacted]	[redacted]	[redacted]
Mean BSA (m^2)	[redacted]	[redacted]	[redacted]	[redacted]
Mean weight (Kg)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSA: body surface area; ITT: intention-to-treat.

B.3.3.2 Transition probabilities

A summary of the transition probabilities used in the economic analysis is presented in the model structure diagram in Figure 30 below, alongside the corresponding sources of transition probabilities provided in Table 45. Unless specified otherwise, the same transition probabilities and assumptions were adopted in all four economic analyses.

Figure 30: Economic analysis model structure diagram including transition probabilities



Abbreviations: DR: distant recurrence; ET: endocrine therapy; IDF: invasive disease free; IDFS: invasive disease-free survival; NMR: non-metastatic recurrence; REM: remission; SPM: secondary primary malignancy.

Table 45: Summary of transition probabilities used in the economic analysis

Starting state	Destination sate	Transition name	Value	Source
iDFS	NMR	iDFS_NMR	NMR % from trial applied to iDFS curve[a]	NATALEE (April 2024 data cut).[79]
	DR	iDFS_DR	DR % from trial applied to iDFS curve[a] Patients transition to the ET-sensitive or ET-resistant	NATALEE (April 2024 data cut).[79]

			substates depending on when they experience a DR	
	SPM	iDFS_SPM	SPM % from trial applied to iDFS curve[a]	NATALEE (April 2024 data cut).[79]
	Death	iDFS_Death	Death % from trial applied to iDFS curve[a]	NATALEE (April 2024 data cut)[79] and UK life tables.
NMR	Remission	NMR_REM	1	After 12 months, all patients transition into the remission health state or die due to all-cause mortality, in line with the approach used to inform decision making in NICE TA632[136] and TA810.[6]
	Death	NMR_Death	Maximum of background mortality or iDFS death rate	NATALEE[79] and UK life tables.
Remission	DR	REM_DR	0.00760	Hamilton *et al.* (2015),[137] in line with the approach used to inform decision making in NICE TA632[136] and TA810.[6] All patients are assumed to transition to the ET-sensitive substate as these patients are modelled to have remained free of DR for at least 12 months following discontinuation of ET.
	Death	REM_Death	Maximum of background mortality or iDFS death rate	NATALEE (April 2024 data cut)[79] and UK life tables.

Footnotes: [a]The iDFS curve was adjusted for mortality and treatment waning assumptions.
Abbreviations: DR: distant recurrence; ET: endocrine therapy; iDFS: invasive disease-free survival; NMR: non-metastatic recurrence; REM: remission; SPM: secondary primary malignancy; TA: Technology Appraisal.

The transition probabilities used in the economic analysis are discussed in more detail below.

iDFS health state

All populations

Across all four economic analyses, the AI arm of the NATALEE trial was used to inform the efficacy of ET. However, as the AI arm of the NATALEE trial does not include patients receiving tamoxifen, an adjustment was made to account for a proportion of patients receiving tamoxifen and reflect the overall efficacy of ET. This adjustment is described in more detail in Section B.3.3.3.

Base case: Population 1 (NATALEE ITT)

For patients receiving ribociclib plus AI and ET in the base case economic analysis (Population 1 [NATALEE ITT]), iDFS transition probabilities (i.e., transitions to SPM, NMR, DR, and death)

were estimated based on parametric survival distributions fit to iDFS data for ribociclib plus AI and AI from the NATALEE trial (Population 1 [NATALEE ITT]; April 2024 data cut-off), respectively.

Full details of the parametric survival distribution curve fitting process for the base case economic analysis are presented in Section B.3.3.3.

Populations 2 and 3 (NATALEE node-positive high-risk and node-negative high-risk)

iDFS transition probabilities for patients receiving ribociclib plus AI and ET in Populations 2 and 3 were derived as per the base case economic analysis, based on parametric survival distributions fit to iDFS data for ribociclib plus AI and AI from the relevant node-positive and node-negative high-risk populations of the NATALEE trial (April 2024 data cut-off), respectively.

Full details of the parametric survival distribution curve fitting process for Populations 2 and 3 are presented in Appendix R.1.2 and Appendix R.1.3, respectively.

Population 4 (node-positive high-risk eligible for abemaciclib)

iDFS for patients receiving ribociclib plus AI and ET in Population 4 (node-positive high-risk eligible for abemaciclib) was based on parametric survival distributions fit to matched and weighted ribociclib plus AI and AI Kaplan-Meier curves from the NATALEE-selected population of the NATALEE trial (April 2024 data cut). These were derived from the MAIC conducted between the relevant subpopulation of the NATALEE trial, and the ITT population of Cohort 1 in the monarchE trial, the pivotal clinical trial for abemaciclib plus ET in this subgroup. Full details of this MAIC are described in Section B.2.8.

Given the non-statistically significant result for iDFS between ribociclib plus AI and abemaciclib plus ET in the MAIC (see Section B.2.8.5), iDFS for patients receiving abemaciclib plus ET in Population 4 (node-positive high-risk eligible for abemaciclib) was assumed equivalent to that of ribociclib plus AI, and therefore a HR of 1 was applied to the matched and weighted ribociclib plus AI Kaplan-Meier curve from the NATALEE-selected population of the NATALEE trial to derive the iDFS curve for abemaciclib plus ET.

Full details of the parametric survival distribution curve fitting process for Population 4 (node-positive high-risk eligible for abemaciclib) are presented in Appendix R.1.4.

Distribution of iDFS events

In each model cycle, the probability of transitioning from iDFS to the SPM, NMR, DR, and death health states was calculated by multiplying the iDFS hazard rate by the distribution of iDFS events by type (i.e., with types of events corresponding to the model health states). Across all four economic analyses, the distribution of iDFS events for ribociclib plus AI and ET was estimated from the ribociclib plus AI and AI arms of the respective populations in the NATALEE trial (April 2024 data cut) (Table 47).

For patients receiving abemaciclib plus ET in Population 4 (node-positive high-risk eligible for abemaciclib), in the absence of any published data, the distribution of iDFS events was assumed to be the same as for ribociclib plus AI. This assumption was validated in October 2024 during follow-up discussions held with three clinical experts (who were in attendance at the September 2024 advisory board).Two clinical experts suggested that they would not expect the distribution

of iDFS events to vary significantly between CDK4/6 inhibitors; One clinical expert noted that it is possible that the distribution of events would differ, however, in the absence of other data it is a reasonable to assume that the event distribution would be the same (see Appendix Q.3).

The distribution of iDFS events was assumed to be constant over time; however, the probabilities of transitioning to the death state were capped for general population mortality, based on age- and sex-matched lifetables. As such, the proportion of transitions from iDFS to death increases over time (i.e., relative to the proportion of transitions into other health states) as the modelled population ages. The distribution of iDFS events by type for each arm of the model in each population are shown in Table 46.

Table 46: Proportion of iDFS events that are SPM, NMR, DR or death from NATALEE

Treatment arm	Number of events	% iDFS events that are NMR (P_{NMR})	% iDFS events that are death (P_{death})	% iDFS events that are DR (P_{DR})	% iDFS events that are SPM (P_{SPM})
Base case (Population 1 [NATALEE ITT population])					
Ribociclib plus AI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Population 2 (NATALEE node-positive high-risk)					
Ribociclib plus AI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Population 3 (NATALEE node-negative high-risk)					
Ribociclib plus AI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Population 4 (node-positive high-risk eligible for abemaciclib)					
Ribociclib plus AI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abemaciclib plus ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AI: aromatase inhibitor; DR: distant recurrence; ET: endocrine therapy; iDFS: invasive disease-free survival; NMR: non-metastatic recurrence; SPM: secondary primary neoplasm.
Source: Novartis Data on File (NATALEE Clinical Study Report April 2024 Data Cut).[79]

Table 47 details how the proportions of events from NATALEE are used to inform the calculations of transition probabilities from the iDFS health state to the NMR, death, DR and SPM health states.

Table 47: Transitions from the iDFS health state based on constant proportions of iDFS events

Starting health state	Proportion to destination state	Transition probabilities or rates
iDFS	iDFS: $S(t)$	Remaining in iDFS: $S(t)$
	NMR: P_{NMR}	iDFS_NMR: $P_{NMR} \times (1 - S(t))$
	SPM: P_{SPM}	iDFS_SPM: $P_{SPM} \times (1 - S(t))$
	DR: P_{DR}	iDFS_DR : $P_{DR} \times (1 - S(t))$
	Death: P_{death}	iDFS_Death: $P_{death} \times (1 - S(t))$

Abbreviations: DR: distant recurrence; iDFS: invasive disease-free survival; NMR: non-metastatic recurrence; SPM: secondary primary neoplasm.

NMR health state

Transition probability from NMR to remission (NMR_REM)

If patients experience an NMR, they transition to the NMR health state, which is a 12-month tunnel state. After 12 months, all patients move to the remission health state, except for those patients who have died. The duration of the NMR tunnel state was informed by the approach used to inform decision making in both TA632[136] and TA810.[6] The overall model structure for this submission, including the 12-month NMR duration assumption, was also validated by clinical experts at an advisory board held by the Company in September 2024 (see Appendix Q.3).

Transition probability from NMR to death (NMR_D)

The probability of death for patients with NMR was assumed to be the same as that for patients in the iDFS or remission health states, capped using age- and sex-matched general population mortality.

Remission health state

Transition probability from remission to distant recurrence (REM_DR)

It was assumed that patients in the remission health state remain in this health state until they experience either DR or death. The monthly transition probability of experiencing a DR was assumed to be 0.00760 (from a mean time to progression of 7.6 years), based on the approach used to inform decision making in NICE TA632[136] and TA810,[6] derived from Hamilton *et al.* (2015),[137] and assumed to remain constant over time. Patients experiencing a DR in the remission health state were assumed to all move to the endocrine-sensitive DR health state, as these patients are modelled to have remained free of DR for at least 12 months following discontinuation of the ET component of each treatment arm.

Transition probability from remission to death (REM_death)

The probability of death for patients in the remission health state was assumed to be the same as that for patients in the iDFS or NMR health states, capped using age- and sex-matched general population mortality.

Distant recurrence health state

As described in Section B.3.2.1 above, the DR substates (ET-sensitive and ET-resistant) were modelled as absorbing health states. Patients who entered these substates were assigned assigned LYs, time on treatment, QALYs, and costs associated with the DR health state, calculated within a PSM framework based on PFS, TTD, and OS data from clinical trials for ribociclib in the advanced or metastatic breast cancer setting (MONALEESA-2 for the ET-sensitive substate and MONALEESA-3 for the ET-resistant substate), supplemented by data from the literature on the efficacy of other subsequent therapies received in the DR health state (see Section B.3.3.3 for further details of how efficacy was modelled in the DR substates).[87, 133]

Full details of the ET-sensitive and ET-resistant PSMs, including the parametric survival distribution curve fitting process, are presented in Appendix S.

B.3.3.3 Parametric survival distributions

The following section describes the fitting of parametric survival distributions for iDFS in the base case economic analysis of ribociclib plus AI vs ET in Population 1 (NATALEE ITT). Details of the

same parametric survival distribution fitting process for each of the subgroup economic analyses are presented in Appendix R.1.

Parametric survival distributions were fit to iDFS data from the NATALEE trial (Population 1 [NATALEE ITT; April 2024 data cut) using FlexSurv, an R package for fully-parametric modelling of survival data.[138] The following parametric distributions were estimated:

- Exponential
- Weibull
- Log-logistic
- Lognormal
- Gompertz
- Generalised gamma
- Gamma
- Generalised F
- Restricted cubic spline (RCS) distributions (up to 3 knots)

For the RCS distributions, Weibull, log-logistic and lognormal distributions were explored. RCS distributions use a single knot (plus the two boundary knots which are always included). The boundary knots are based on the minimum and maximum failure time. The non-boundary knot is based on the median of the failure times.

The distributions used in the base case cost-utility analysis were selected following the guidance set out in NICE DSU TSD 14, based on a number of factors including model fit statistics, visual inspection of survival distributions, hazard functions, time dependent HRs, and diagnostic plots for treatment effects, as well as clinical plausibility.[139] The Bayesian Information Criterion (BIC) was used as the primary measure of statistical fit. Plots of Schoenfeld residuals were generated to assess the proportional hazards assumption; further details of the proportional hazards tests are presented in Appendix R.

Survival distributions for iDFS and TTD for ribociclib plus AI and ET were estimated using two alternative approaches for parameterising the effect of treatment on iDFS times:

- “Restricted” models in which a single parameter of the survival distribution is allowed to differ between treatment arms
- “Unrestricted” models in which all parameters of the survival distribution are allowed to differ between treatment arms

With both approaches, the distributions of survival for the two treatment arms were assumed to be of the same class (e.g. both are Weibull). However, with the first approach (restricted models), in which the effect of treatment is restricted to a single distributional parameter (e.g. the scale parameter of the Weibull distribution), projections of survival are consistent with proportional hazards, accelerated failure time, or other univariate treatment effect models, depending on the underlying distribution (e.g. the Gompertz is a proportional hazards model, the lognormal and log-logistic are accelerated failure time models, and the exponential and Weibull are both proportional hazards and accelerated failure time models). The second approach (unrestricted models) places no such restrictions on the distributional parameters or the assumed nature of

treatment effect within the class of distributions. The use of this approach for parameterising treatment effects permits the comparison of models in which the effect of treatment is and is not interacted on different distributional parameters using conventional fit statistics such as the BIC.

Invasive disease-free survival

The probability of iDFS events for patients receiving ribociclib plus AI and ET in Population 1 (NATALEE ITT) were based on the ribociclib plus AI and AI arms of the NATALEE trial (ITT population; April 2024 data cut). Parametric distributions fit to the iDFS data were evaluated based on the criteria described in Section B.3.3.3.

Full details of the proportional hazards testing for iDFS are reported in Appendix R.1. In the transformation and treatment effect diagnostic plots for iDFS, plots of the –ln(survival) vs months, representing the cumulative hazard function, are straight lines for the most part, suggesting relatively constant hazards. In the Schoenfeld residuals test, the curve was virtually a straight line and the p-value on the test of non-proportionality (0.538) was not significant suggesting that the PH assumption is reasonable.

A ranking of parametric distributions for iDFS based on the fit statistics are shown in Figure 31. The top six distributions according to BIC statistic were as follows:

- Exponential
- Log-logistic (R)
- Gamma (R)
- Weibull (R)
- Gompertz (R)

The exponential distribution had the best statistical fit based on the BIC, though the range of BICs among the top six best-fitting distributions was 11 (8,157.30 for exponential to 8,168.00 for RCS Weibull restricted). It is not unexpected that the exponential distribution is ranked higher with BIC than with AIC and AICc as the BIC metric places a higher penalty on the number of parameters than the latter; the exponential distribution has only one parameter.

Figure 31: Fit statistics for parametric distributions fit to iDFS for Population 1 (NATALEE ITT)

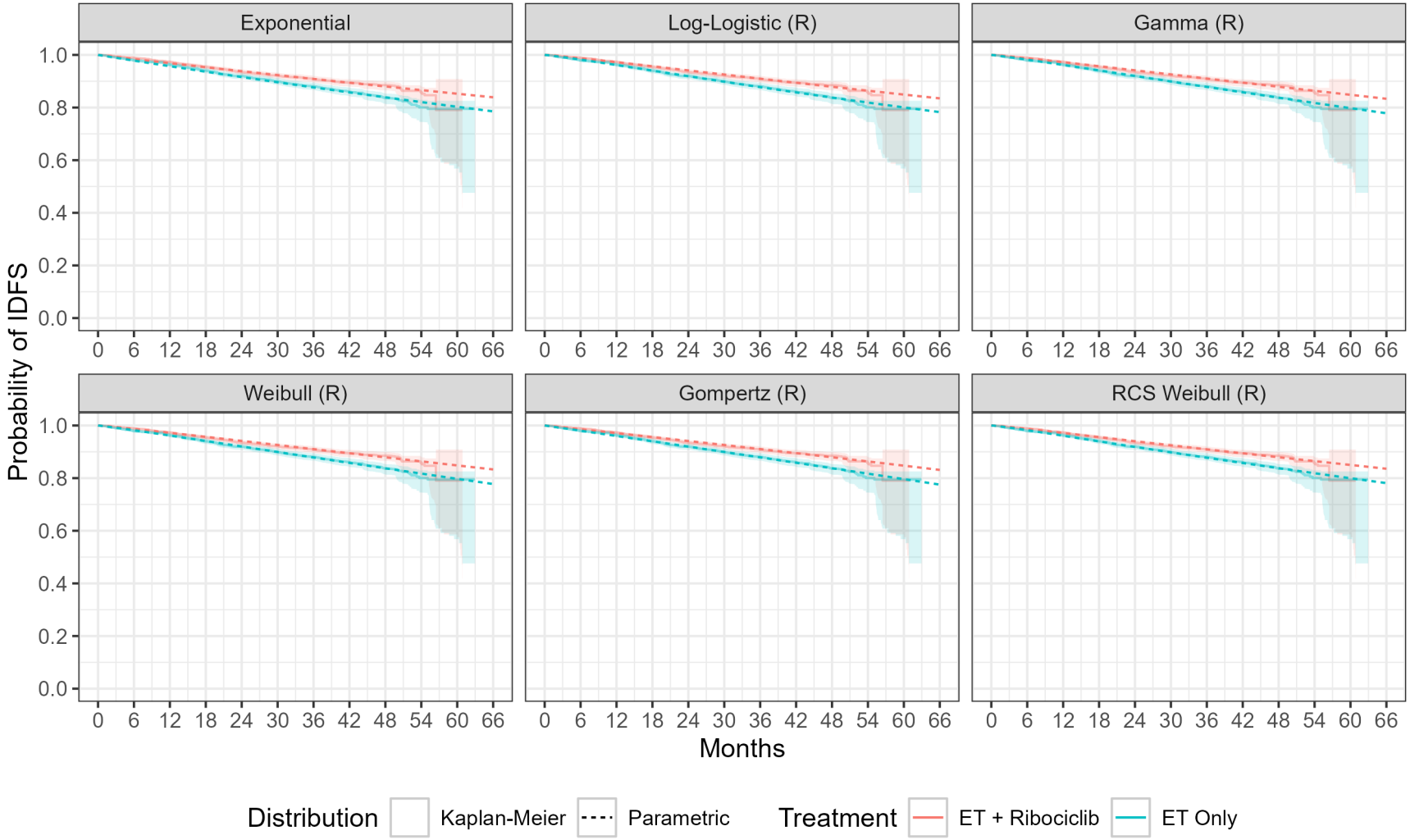
Distribution	AIC	AICc	BIC
Exponential	8,144.30	8,144.30	8,157.30
Log-logistic (R)	8,140.60	8,140.60	8,160.20
Gamma (R)	8,140.80	8,140.80	8,160.40
Weibull (R)	8,141.00	8,141.00	8,160.60
Gompertz (R)	8,143.70	8,143.70	8,163.30
RCS Weibull (R)	8,141.80	8,141.80	8,168.00
Generalised gamma (R)	8,142.20	8,142.20	8,168.40
RCS Log-logistic (R)	8,142.30	8,142.30	8,168.40
Log-logistic (U)	8,142.60	8,142.60	8,168.80
Gamma (U)	8,142.80	8,142.80	8,169.00
Weibull (U)	8,143.00	8,143.00	8,169.20

Distribution	AIC	AICc	BIC
Lognormal (R)	8,151.20	8,151.20	8,170.80
Gompertz (U)	8,145.30	8,145.30	8,171.50
Generalised F (R)	8,144.20	8,144.20	8,176.90
Lognormal (U)	8,153.00	8,153.00	8,179.20
RCS Weibull (U)	8,144.40	8,144.40	8,183.60
Generalised gamma (U)	8,144.60	8,144.70	8,183.90
RCS Log-logistic (U)	8,144.70	8,144.70	8,183.90
Generalised F (U)	8,148.60	8,148.70	8,200.90

Footnotes: A smaller BIC is better. The AI arm of the NATALEE trial was used to inform the efficacy of ET, with an adjustment to account for the efficacy of tamoxifen.
Abbreviations: AI: aromatase inhibitor; AIC: Akaike Information Criterion; AICc: corrected Akaike Information Criterion; BIC: Bayesian Information Criterion; ET: endocrine therapy; iDFS: invasive disease-free survival; ITT: intention-to-treat; R: restricted; RCS: restricted cubic splines; U: unrestricted.

Parametric survival distributions for iDFS in Population 1 (NATALEE ITT) during the trial period for the best-fitting distributions based on BIC are shown in Figure 32. The visual fit of the parametric distributions to the Kaplan-Meier curves are all reasonably good and very similar in fit. All the fitted distributions are within the 95% CIs for the Kaplan-Meier distributions throughout the trial follow-up to the point where it is difficult to say that one distribution has better visual fit compared with the others.

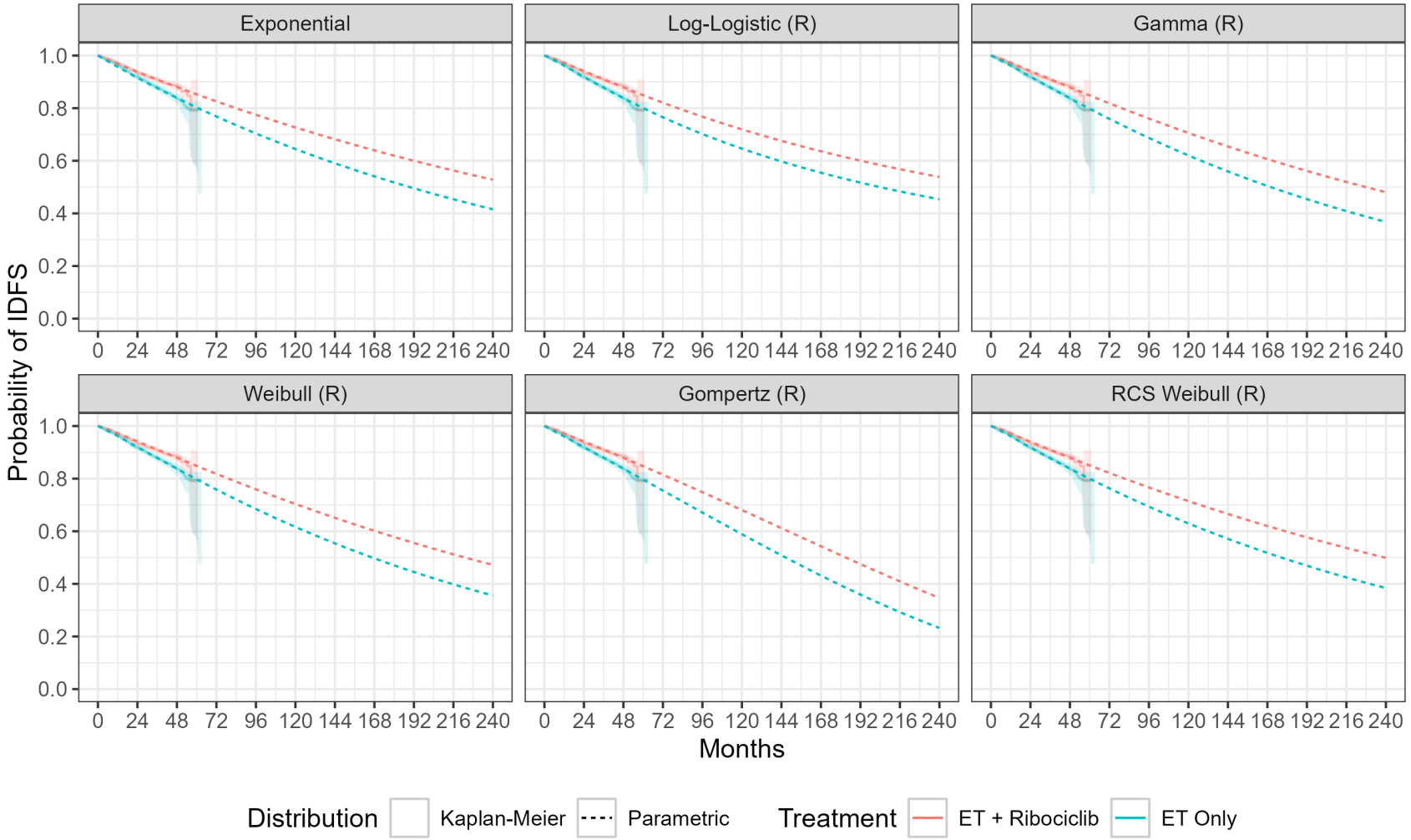
Figure 32: Parametric survival distributions fit to iDFS for Population 1 (NATALEE ITT), by randomised treatment



Footnotes: Best fitting distributions based on BIC are shown. Distributions are ranks by BIC (left to right, top to bottom).
Abbreviations: BIC: Bayesian Information Criterion; iDFS: invasive disease-free survival; ITT: intention-to-treat; R: restricted; RCS: restricted cubic splines; U: unrestricted.

Long-term projections of iDFS (out to 20 years) in Population 1 (NATALEE ITT) for these distributions are shown in Figure 33. Five of the best fitting parametric distributions according to BIC (exponential, log-logistic restricted, gamma restricted, Weibull restricted, and RCS Weibull restricted) yield very similar long-term projections, with projected iDFS for ribociclib plus AI at approximately 50% by 20 years and 35% to 40% for ET. The restricted Gompertz distribution yields much lower long-term survival projections than the other top fitting distributions, with survival at 20 years approximately 10% lower for either arm compared with the other distributions shown. It should be noted that these projections do not incorporate non-EBC mortality, which is captured separately within the model.

Figure 33: Long-term projections of iDFS based on parametric survival distributions fit to iDFS for Population 1 (NATALEE ITT), by randomised treatment



Footnotes: Best fitting distributions based on BIC are shown. Distributions are ranks by BIC (left to right, top to bottom).
Abbreviations: BIC: Bayesian Information Criterion; iDFS: invasive disease-free survival; ITT: intention-to-treat; R: restricted; RCS: restricted cubic splines; U: unrestricted.

Lacking data on long-term iDFS for a population consistent with the NATALEE trial, iDFS curve selection was based on visual fit and statistical goodness-of-fit, but primarily on clinical plausibility.

Given the visual fits of the parametric distributions to the iDFS Kaplan-Meier curves were all reasonably good, the exponential distribution, the best statistically fitting model, was selected to model iDFS in the base case economic analysis in Population 1 (NATALEE ITT) based on clinical plausibility as described below.

Clinical expert opinion was sought for the extrapolation of the iDFS curves for ribociclib plus AI and ET in Population 2 (NATALEE node-positive high-risk) and Population 3 (NATALEE node-negative high-risk) (see Appendix Q.3), which together comprise the full Population 1 (NATALEE ITT). As such, the long-term iDFS extrapolation with the exponential curve for Population 1 (NATALEE ITT) was chosen as it sat between the long-term iDFS estimates deemed clinically plausible for Population 2 and Population 3 (see Appendix R.1).

The second and third best statistically-fitting parametric distributions according to BIC, log-logistic (R) and gamma (R), respectively, were explored in scenario analyses (see Section B.3.11).

Adjustment to AI arm of NATALEE to inform efficacy of ET

Across all four economic analyses, the AI arm of the NATALEE trial was used to inform the efficacy of ET. However, as the AI arm of the NATALEE trial does not include tamoxifen or exemestane, which are also considered standard ETs in UK clinical practice, a weighted average HR was applied to the AI iDFS curve from NATALEE to reflect any differential efficacy for the proportion of patents receiving these therapies, as detailed below:

- **Tamoxifen:** as detailed in Section B.1.3.4, there is a wealth of evidence demonstrating that AIs are more effective than tamoxifen at reducing disease recurrence in EBC (see Appendix M.1). The reduced efficacy of tamoxifen vs AIs was also validated by UK clinical experts at a recent advisory board held in September 2024 (see Appendix Q.3).
    - A HR of 1.10 for tamoxifen vs AIs was sourced from a meta-analysis published by Liao et al. (2022),[101] identified in a TLR (Appendix M.1), and applied to the AI arm. This analysis compared the efficacy and safety of different five-year regimens of initial adjuvant ET (including AIs and tamoxifen) among postmenopausal patients with HR+ EBC.[101] An alternative HR (1.45), derived from a study by Janni et al. (2023)[140] was explored in a scenario analysis in all four populations. Whilst this study was not identified in the TLR (because it is a conference presentation), it represents a recent, comprehensive meta-analysis comparing the efficacy of tamoxifen to AIs in HR+/HER2– EBC.
    - Additionally, a further scenario analysis was conducted in all four populations where the HR for tamoxifen vs AIs was set to 1 (thereby assuming equal efficacy) as a conservative assumption
- **Exemestane:** all AIs were assumed to have equivalent efficacy, as validated by clinical experts at the Company advisory board held in September 2024 (see Appendix Q.3) and therefore a HR of 1 was applied for the proportion of patients assumed to receive exemestane

Based on the treatment distribution for ET and the proportion of patients estimated to receive tamoxifen (Populations 1–3: [redacted], Population 4: [redacted]; see Section B.3.5.1) a weighted average

HR was then applied to the parametric survival distribution for the AI arm of the NATALEE trial.

Time to treatment discontinuation

The following section describes the fitting of parametric survival distributions for TTD in the base case analysis of ribociclib plus AI vs ET in Population 1 (NATALEE ITT). Details of the same parametric survival distribution fitting process for TTD in each of the economic subgroup analyses populations are presented in Appendix R.2.

Patients in the iDFS state were partitioned as being either on- and off-treatment, using the TTD curve from the NATALEE trial (ITT population). TTD was estimated independently for ribociclib plus AI and ET using patient-level data from the NATALEE trial (the ribociclib plus AI and AI arms, respectively). Therefore, for patients receiving ribociclib plus AI, the model includes one TTD curve to estimate time on treatment with ribociclib and a separate TTD curve to estimate time on treatment with AI. This reflects a component of the NATALEE trial design whereby patients who discontinued ribociclib or placebo could continue receiving treatment with AI.

TTD was not a pre-defined endpoint in NATALEE and was calculated based on *post hoc* analyses of patient-level exposure data from the April 2024 data cut. TTD was defined as the time from randomisation until the last date of treatment exposure for patients who permanently discontinued, with events defined based on the following: patient decision to discontinue treatment, AEs, disease relapse, ET discontinuation, physician decision, lost to follow-up, withdrawal from the study, protocol deviation or for 'other' reasons.

Patients who were still receiving treatment by the data cut-off date were censored for TTD at the date of censoring for iDFS.

Ribociclib

Given the maturity of the TTD data, and the maximum 3-year treatment duration of ribociclib, TTD for ribociclib across all four economic analyses was based directly on the Kaplan-Meier curve for TTD from the NATALEE trial (April 2024 data cut). The Kaplan-Meier curve for TTD for ribociclib in Population 1 (NATALEE ITT) is presented below in Figure 34.

Figure 34: Kaplan-Meier curve for TTD for ribociclib in Population 1 (NATALEE ITT)

Abbreviations: TTD: time-to-treatment discontinuation.

AI (in combination with ribociclib) and ET

Probabilities of TTD events for patients receiving AI in combination with ribociclib, and ET in Population 1 (NATALEE ITT), were also estimated using patient-level data from the NATALEE trial (ITT population). Whilst the maximum duration of treatment with AI/ET in the base case was assumed to be 5 years, based on the NATALEE trial design, feedback from UK clinical experts indicated that treatment with AI/ET can may continue beyond 5 years (see Appendix Q.2). As such, the duration of the NATALEE trial follow-up was not considered sufficient to capture all treatment discontinuation related to the use of AI/ET. For this reason, parametric survival distributions were fit to patient-level data on TTD and these were evaluated based on the criteria described in Section B.3.3.3.

Full details of the proportional hazards testing for TTD are reported in Appendix R.2. In the transformation and treatment effect diagnostic plots for TTD, plots of the –ln(survival) vs months, representing the cumulative hazard function, the curves appear to be parallel throughout follow-up, suggesting the proportional hazards assumption is reasonable. In the Schoenfeld residuals test, the curve was virtually a straight line and the p-value on the test of non-proportionality was not significant suggesting that the PH assumption is not unreasonable.

A ranking of parametric distributions fit to TTD for AI/ET for Population 1 (NATALEE ITT) by the fit statistics are shown in Figure 35. The top six distributions, according to BIC statistic were as follows:

- Weibull (R)
- Gamma (R)
- Log-logistic (R)
- RCS Weibull (R)
- Weibull (U)

- Generalised gamma (R)

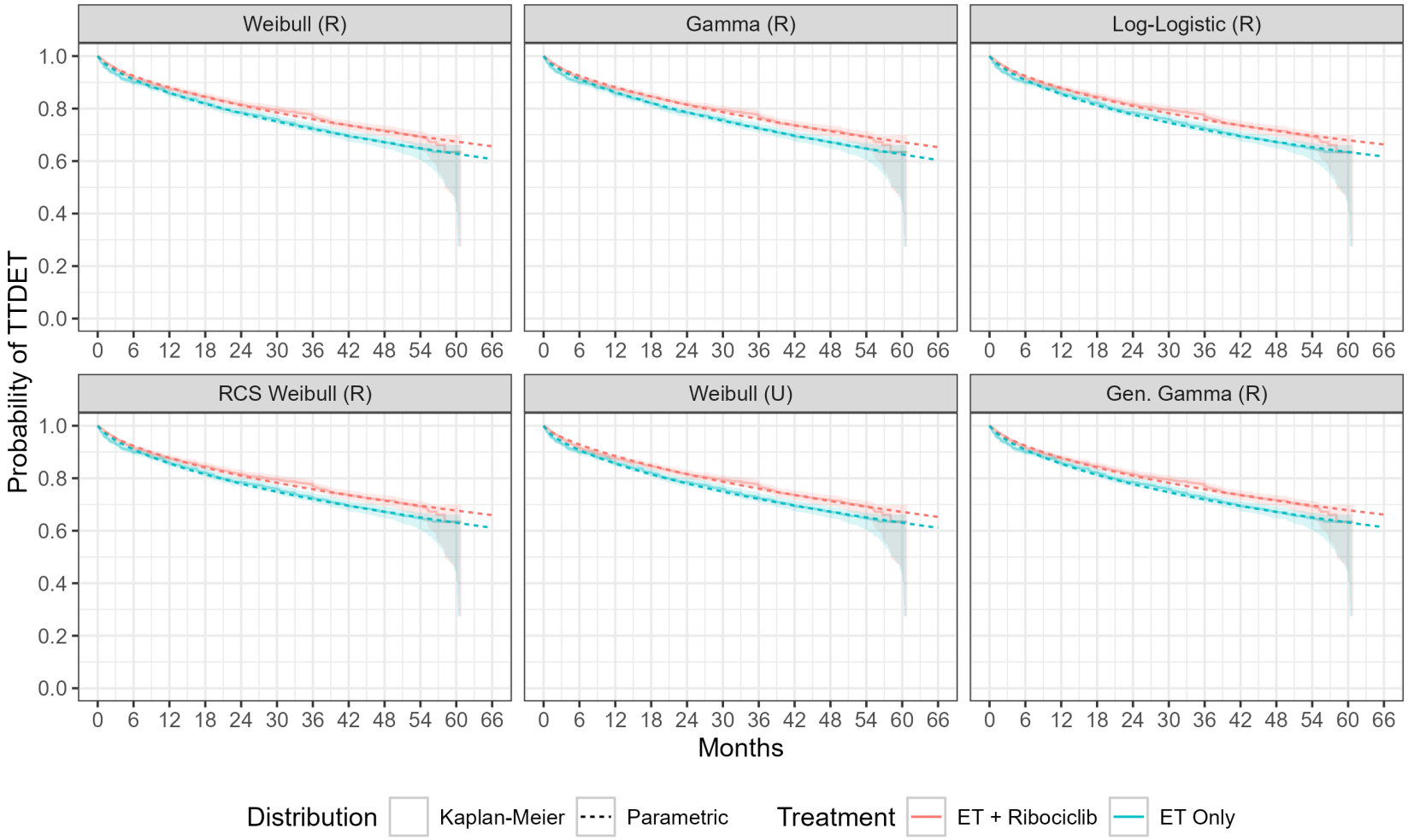
Figure 35: Fit statistics for parametric distributions fit to AI/ET TTD for Population 1 (NATALEE ITT)

Distribution	AIC	AICc	BIC
Weibull (R)	17,587.20	17,587.20	17,606.90
Gamma (R)	17,589.10	17,589.10	17,608.70
Log-logistic (R)	17,592.00	17,592.00	17,611.60
RCS Weibull (R)	17,586.00	17,586.00	17,612.10
Weibull (U)	17,586.70	17,586.70	17,612.80
Generalised gamma (R)	17,587.40	17,587.40	17,613.60
Gamma (U)	17,588.10	17,588.10	17,614.30
RCS Lognormal (R)	17,589.00	17,589.00	17,615.10
Log-logistic (U)	17,591.90	17,591.90	17,618.10
RCS Log-logistic (R)	17,594.00	17,594.00	17,620.20
Generalised F (R)	17,589.50	17,589.60	17,622.20
RCS Weibull (U)	17,584.50	17,584.50	17,623.70
Generalised gamma (U)	17,585.60	17,585.60	17,624.80
Lognormal (R)	17,609.20	17,609.20	17,628.80
RCS Lognormal (U)	17,589.90	17,589.90	17,629.10
RCS Log-logistic (U)	17,593.20	17,593.20	17,632.40
Lognormal (U)	17,608.50	17,608.50	17,634.70
Generalised F (U)	17,589.70	17,589.70	17,642.00
Gompertz (R)	17,690.10	17,690.10	17,709.70
Gompertz (U)	17,691.50	17,691.50	17,717.60
Exponential	17,827.60	17,827.60	17,840.70

Footnotes: A smaller BIC is better.
The AI arm of the NATALEE trial was used to inform the efficacy of ET, with an adjustment to account for the efficacy of tamoxifen.
Abbreviations: AI: aromatase inhibitor; AIC: Akaike Information Criterion; AICc: corrected Akaike Information Criterion; BIC: Bayesian Information Criterion; ET: endocrine therapy; ITT: intention-to-treat; R: restricted; RCS: restricted cubic splines; TTD: time to treatment discontinuation; U: unrestricted.

Parametric survival distributions for AI/ET TTD during the trial period for the best-fitting distributions based on BIC are shown in Figure 36. The visual fit of the parametric distributions to the Kaplan-Meier curves are all reasonably good.

Figure 36: Parametric survival distributions fit to AI/ET TTD for Population 1 (NATALEE ITT), by randomised treatment



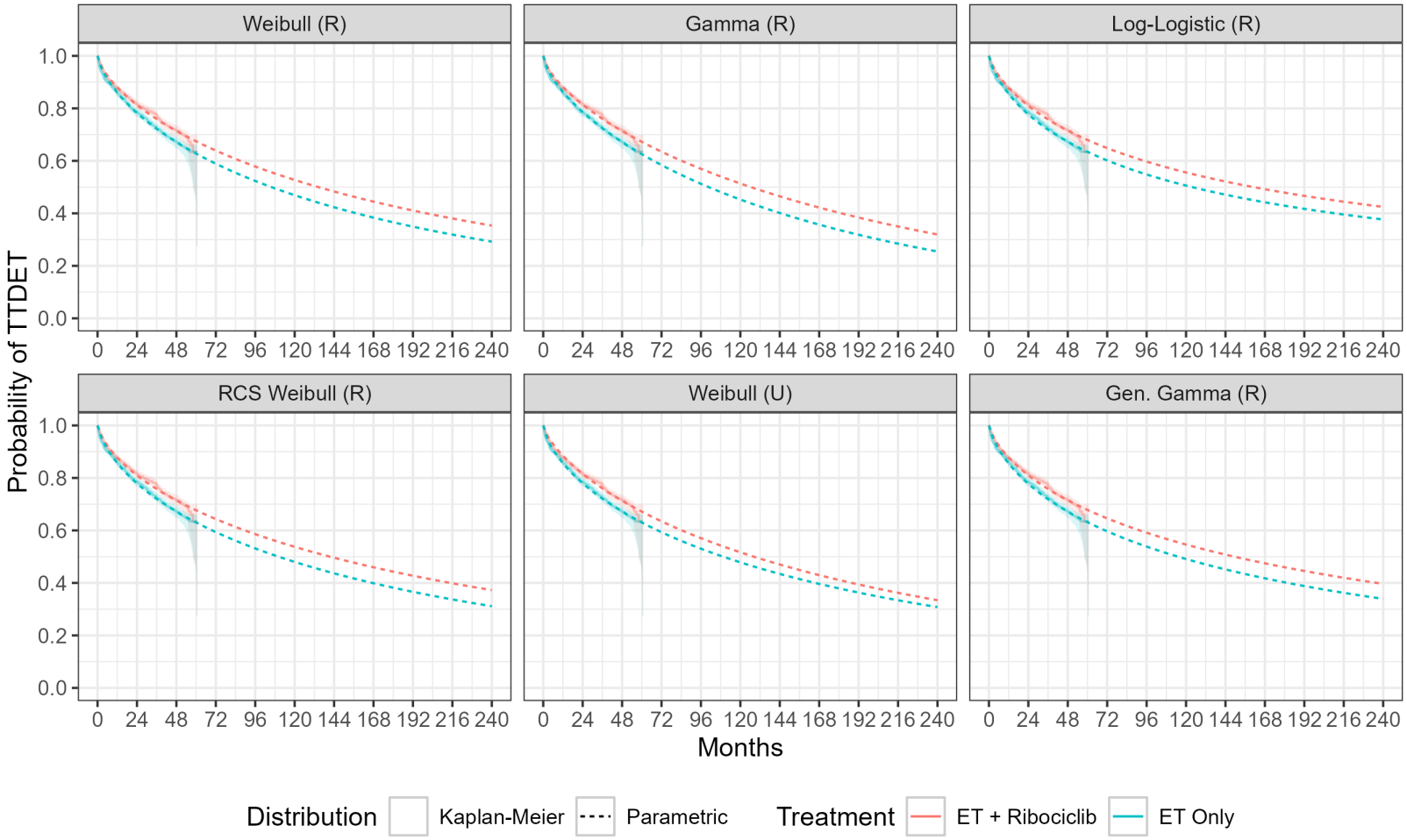
Footnotes: Best fitting distributions based on BIC are shown. Distributions are ranks by BIC (left to right, top to bottom).
The AI arm of the NATALEE trial was used to inform the efficacy of ET, with an adjustment to account for the efficacy of tamoxifen.
Abbreviations: AI: aromatase inhibitor; BIC: Bayesian Information Criterion; ET: endocrine therapy; ITT: intention-to-treat; R: restricted; RCS: restricted cubic spline; RIBO: ribociclib; TTD: time to treatment discontinuation; TTDET: time to treatment discontinuation of endocrine therapy; U: unrestricted.

Long-term projections of TTD (out to 20 years) for AI/ET in Population 1 (NATALEE ITT) for the above distributions are shown in Figure 37.

Curve selection for TTD ET was based on visual fit and statistical goodness-of-fit, but primarily on clinical plausibility, and the assumption that treatment duration with ET would be no longer than 5 years in the base case. The two best fitting models based on the BIC were the Weibull (R) and gamma (R) distributions. Both of these models also had excellent visual fit to the observed TTD during follow-up. Given that treatment with AI/ET was assumed to last no longer than 5 years in the base case, consistent with the design of the NATALEE trial, both of these distributions would yield nearly identical TTD estimates if utilised in the model. Based on these considerations, and given that the Weibull (R) model had a better fit based on BIC, this distribution was selected to model AI/ET TTD in the base case economic analysis for Population 1 (NATALEE ITT). As the second-best fitting parametric survival distribution, the gamma (R) distribution was explored in a scenario analysis.

Scenario analyses were also conducted to explore the impact of increasing the maximum treatment duration of AI/ET to 7 years and 10 years, based on UK clinical expert feedback (see Appendix Q.2).

Figure 37: Long-term projections of AI/ET TTD based on parametric survival distributions fit to TTD for Population 1 (NATALEE ITT), by randomised treatment



Footnotes: Best fitting distributions based on BIC are shown. Distributions are ranks by BIC (left to right, top to bottom).
The AI arm of the NATALEE trial was used to inform the efficacy of ET, with an adjustment to account for the efficacy of tamoxifen.
Abbreviations: AI: aromatase inhibitor; BIC: Bayesian Information Criterion; ET: endocrine therapy; ITT: intention-to-treat; R: restricted; RCS: restricted cubic spline; RIBO: ribociclib; TTD: time to treatment discontinuation; TTDET: time to treatment discontinuation of endocrine therapy; U: unrestricted.

Summary

A summary of the extrapolations for iDFS and TTD for ribociclib plus AI and the relevant comparators across the four economic analyses is provided in Table 48. Full details of the parametric survival curve selection process for Populations 2–4 are presented in Appendix R.

Table 48: Summary of extrapolations for iDFS and TTD across all four economic analyses

Treatment arm	Base case extrapolation for iDFS	Scenario analysis extrapolations for iDFS	Base case extrapolation for TTD	Scenario analysis extrapolations for TTD
Base case (Population 1 [NATALEE ITT])				
Ribociclib plus AI	Exponential	• Log-logistic (R) • Gamma (R)	• Ribociclib: TTD Kaplan-Meier curve • AI: Weibull (R)	• Ribociclib: N/A • AI: Gamma (R)
ET	Exponential	• Log-logistic (R) • Gamma (R)	• Weibull (R)	• AI: Gamma (R)
Population 2 (NATALEE node-positive high-risk)				
Ribociclib plus AI	Exponential	• Gamma (U) • Weibull (U)	• Ribociclib: TTD Kaplan-Meier curve • AI: Weibull (R)	• Ribociclib: N/A • AI: Log-logistic (R)
ET	Exponential	• Gamma (U) • Weibull (U)	• Weibull (R)	• Log-logistic (R)
Population 3 (NATALEE node-negative high-risk)				
Ribociclib plus AI	RCS Log-logistic (U)	• Generalised gamma (U) • Generalised F (U)	• Ribociclib: TTD Kaplan-Meier curve • AI: Gamma (R)	• Ribociclib: N/A • AI: Weibull (R)
ET	RCS Log-logistic (U)	• Generalised gamma (U) • Generalised F (U)	• Gamma (R)	• Weibull (R)
Population 4 (node-positive high-risk eligible for abemaciclib)				
Ribociclib plus AI	Exponential (MAIC)	• Gamma (U) (MAIC) • Gamma (R) (MAIC)	• Ribociclib: TTD Kaplan-Meier curve • AI: Lognormal (R)	• Ribociclib: N/A • AI: RCS Lognormal (R)
Abemaciclib plus ET	Assumed equivalent to ribociclib plus AI	• As per scenario analyses for ribociclib plus AI	• Abemaciclib: monarchE TTD Kaplan-Meier curve (Rugo *et al*. [2022])[141] • AI: Lognormal (R)	• Abemaciclib: using ribociclib TTD Kaplan-Meier curve (Population 4) with 2-year maximum treatment duration • ET: RCS Lognormal (R)
ET	Exponential (MAIC)	• Gamma (U) (MAIC) • Gamma (R) (MAIC)	• Lognormal (R)	• RCS Lognormal (R)

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; iDFS: invasive disease-free survival; MAIC: matching adjusted indirect comparison; R: restricted; RCS: restricted cubic splines; TTD: time-to-treatment discontinuation; U: unrestricted.

Distant recurrence

ET-sensitive substate

Patients with advanced or metastatic recurrence >12 months after completing adjuvant ET were assumed to enter the ET-sensitive DR substate. Patients in the ET-sensitive substate were modelled to receive a range of treatments, depending on the treatment received in the adjuvant setting (ribociclib plus AI, ET or abemaciclib plus ET [for Population 4 only]) with the treatment mix informed by clinical expert feedback (see Section B.3.5.2).

For patients receiving ribociclib plus AI as a subsequent treatment in the ET-sensitive substate, PFS, OS and TTD were estimated by fitting parametric survival distributions to individual patient-level data for the ribociclib plus AI arm of MONALEESA-2 (data cut-off June 2021).[87]

For patients receiving other subsequent therapies in the ET-sensitive substate, survival curves were estimated by applying estimated HRs for PFS and OS for the given therapy vs ribociclib plus AI to the corresponding survival curve for ribociclib plus AI. TTD was assumed to equal PFS. The HRs for PFS and OS for other subsequent therapies vs ribociclib plus AI were estimated based on the published NMA by Shao *et al.* (2024),[142] which was identified by the TLR described in Appendix M.1.[142] For capecitabine, which was not represented in the NMA by Shao *et al.* (2024),[142] OS and PFS HRs were derived from the RIGHT CHOICE trial.[143] Despite the RIGHT CHOICE trial being in patients with aggressive breast cancer specifically, in October 2024 clinical experts advised that in the absence of an alternative source of data, it was reasonable to use the results of this study to inform the efficacy of capecitabine in advanced or metastatic breast cancer (see Appendix Q.3). Nevertheless, a scenario analysis was conducted to explore the impact of any uncertainty surrounding the HRs adopted for capecitabine in this setting. The results of this scenario analysis are presented in Section B.3.11 for Population 1 (NATALEE ITT), and Sections B.3.12.1–B.3.12.3 for the Populations 2–4. Full details of the extrapolated curves and the NMA mentioned here, including all HR estimates, are provided in Appendix S.

ET-resistant substate

Patients with advanced or metastatic recurrence ≤12 months from completing adjuvant ET were assumed to enter the ET-resistant DR substate.

For patients receiving ribociclib plus fulvestrant in the ET-resistant substate, extrapolated survival curves for PFS, OS and TTD were estimated by fitting parametric survival distributions to individual patient-level data for the ribociclib plus fulvestrant arm of MONALEESA-3 Group B (data cut-off: January 2022). MONALEESA-3 compared ribociclib plus fulvestrant to fulvestrant alone in men and postmenopausal women with HR+/HER2– advanced or metastatic breast cancer and who have received no more than one prior ET for advanced or metastatic disease. Group B (n=346) included patients with relapse on or within 12 months from completion of [neo]adjuvant ET and no ET for advanced or metastatic breast cancer (n=207) and those with one prior line of ET for advanced or metastatic breast cancer (n=139).[133]

For patients receiving other subsequent therapies in the ET-resistant substate, survival curves were estimated by applying estimated HRs for PFS and OS for the given subsequent therapy vs ribociclib plus fulvestrant to the corresponding survival curve for ribociclib plus fulvestrant. TTD was assumed to equal PFS. As for the ET-sensitive substate, HRs for PFS and OS for other subsequent therapies vs ribociclib plus AI were estimated based on the published NMA by Shao

et al. (2024).[142] The NMA by Shao *et al.* (2024)[142] included all relevant subsequent therapies anticipated to be received in the DR-resistant substate. Full details of the extrapolated curves and the NMA mentioned here, including all HR estimates, are provided in Appendix S.

A summary of the curve choices adopted in the ET-sensitive and ET-resistant substates is presented below in Table 48. In most cases, curve choices were selected based on statistical fit. Details of curve choices, including where selection was not based solely on statistical fit, are detailed in Appendix S.

Table 49: Summary of extrapolations for PFS, OS and TTD in the DR health states

	Treatment arm	Base case extrapolation for PFS	Scenario analysis extrapolations for PFS	Base case extrapolation for OS	Scenario analysis extrapolations for OS	Base case extrapolation for TTD backbone[a]	Scenario analysis extrapolations for TTD
ET-sensitive	Ribociclib plus AI	Lognormal	Exponential	Log-logistic	Gamma	Exponential	Weibull
ET-resistant	Ribociclib plus fulvestrant	Lognormal (R)	Lognormal (U)	Loglogistic (R)	Weibull (R)	Gompertz (R)	RCS Weibull (R)

Footnotes: [a] TTD for monotherapies and add-on AI/ET was assumed to equal PFS.
Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; iDFS: invasive disease-free survival; RCS: restricted cubic splines; TTD: time-to-treatment discontinuation.

B.3.3.4 Treatment effect waning

Based on the results of the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial,[134] treatment effect waning was implemented within the base case economic analysis and all three subgroup economic analyses for ribociclib plus AI, as well as for abemaciclib plus ET in Population 4 (node-positive high-risk eligible for abemaciclib).

The ATAC trial demonstrated falling recurrence rates for HR+ patients on anastrozole vs tamoxifen over time with a “carryover benefit” lasting up to 8 years, following which the treatment effect was shown to wane.[134] As such, treatment effect waning was implemented in the economic model for iDFS from 8 years, an approach consistent with that used to inform decision making in TA810.[6] This approach was also deemed clinically plausible by clinical experts at the September 2024 advisory board, given there remains an absence of longer follow-up data from other clinical trials reporting specifically on patients with HER2− status (see Appendix Q.3). Clinical experts noted that they might expect the “carryover benefit” to last between 5–10 years (see Appendix Q.3).

Treatment effect waning was implemented such that the hazard of recurrence for ribociclib plus ET in iDFS linearly approached that of ET alone over a specified waning duration period. Specifically, the hazard rate for ribociclib after 8 years was calculated as a weighted average of the hazard rate from the parameterised ribociclib plus AI iDFS curve and that of the ET alone iDFS curve. The weights were adjusted during the specified waning period such that the weight applied to the hazard rates of the ET alone arm was equal to one at the end of the waning period. Following the approach in TA810, the end of the waning period was specified to be the

point at which the iDFS event rate was equal to general population mortality.[6]

The following scenario analyses were conducted to explore the impact of the treatment waning assumptions across all four economic analyses for ribociclib plus AI, as well as for abemaciclib plus ET in Population 4 (node-positive high-risk eligible for abemaciclib):

- A constant life-long treatment effect
- A 5-year constant treatment effect, followed by treatment effect waning as per the base case
- A 10-year constant treatment effect, followed by treatment effect waning as per the base case
- A 5-year constant treatment effect, with treatment effect waning from Years 5–8

B.3.3.5 Adverse events

AEs considered in the model included all-cause grade 3+ AEs with an incidence ≥5% for any of the comparators of interest. Grade 1–2 events were not considered because they are generally self-limiting and are therefore not likely to be associated with substantial treatment costs or reductions in HRQoL.

In the base case economic analysis for Population 1 (NATALEE ITT), the incidence of AEs for patients receiving ribociclib plus AI and ET were based on data the ribociclib plus AI and AI arms of the NATALEE trial (ITT population; April 2024 data cut), respectively (Table 50).[79]

In the subgroup economic analyses, the incidence of AEs for patients receiving ribociclib plus AI and ET were based on data from the ribociclib plus AI and AI arms of the respective NATALEE subgroup populations (April 2024 data cut).[79] For the subgroup economic analysis in Population 4 (node-positive high-risk eligible for abemaciclib), the incidence of AEs for patients receiving abemaciclib plus ET were based on the monarchE trial.[108]

Table 50: Grade 3+ AEs from the NATALEE trial included in the economic analyses

AE	Ribociclib plus AI	ET[a]	Abemaciclib plus ET
Base case: Population 1 (NATALEE ITT)			
Alanine aminotransferase increased	[redacted]	[redacted]	--
Diarrhoea	0.63%	0.12%	--
Leukopenia	[redacted]	[redacted]	--
Lymphopenia	[redacted]	[redacted]	--
Neutropenia	[redacted]	[redacted]	--
Population 2 (NATALEE node-positive high-risk)			
Alanine aminotransferase increased	[redacted]	[redacted]	--
Diarrhoea	[redacted]	[redacted]	--
Leukopenia	[redacted]	[redacted]	--
Lymphopenia	[redacted]	[redacted]	--
Neutropenia	[redacted]	[redacted]	--
Population 3 (NATALEE node-negative high-risk)			
Alanine aminotransferase increased	[redacted]	[redacted]	--

AE	Ribociclib plus AI	ET[a]	Abemaciclib plus ET
Diarrhoea	[redacted]	[redacted]	--
Leukopenia	[redacted]	[redacted]	--
Lymphopenia	[redacted]	[redacted]	--
Neutropenia	[redacted]	[redacted]	--
Population 4 (node-positive high-risk eligible for abemaciclib)			
Alanine aminotransferase increased	[redacted]	[redacted]	2.76%
Diarrhoea	[redacted]	[redacted]	7.85%
Leukopenia	[redacted]	[redacted]	11.39%
Lymphopenia	[redacted]	[redacted]	5.41%
Neutropenia	[redacted]	[redacted]	19.63%

Footnotes: [a]The AI arm of the NATALEE trial was used to inform the efficacy of ET.
Abbreviations: AE: adverse event; AI: aromatase inhibitor; ET: endocrine therapy; ITT: intention-to-treat.
Source: Novartis Data on File (NATALEE Clinical Study Report April 2024 Data Cut: Table 4-6);[79] Johnston *et al.* (2023).[108]

B.3.4 Measurement and valuation of health effects

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

In the NATALEE trial, EQ-5D-5L assessments were collected every 12 weeks for the first 24 months followed by every 24 weeks until disease recurrence. An assessment was also taken upon confirmation of first recurrence, upon confirmation of a distant recurrence (if first recurrence was not a distant recurrence), at the last end of treatment visit (upon discontinuation of all study treatments), and for 12 months after confirmation of a DR. Following discontinuation of all study treatments, if a patient failed to return for their assessment, the investigator was required to make every reasonable effort to contact the patient.

Health state utility values for all four economic analyses were estimated from EQ-5D-5L data collected from the ITT population of NATALEE (April 2024 data cut). Dimension scores for the 5 domains of the EQ-5D-5L were converted to index utility scores based on the UK tariff using the 'eq5d' package in R. Mean and standard deviations (SD) for EQ-5D-5L index utility values at baseline and follow-up assessments from the NATALEE ITT population are summarised in Table 51 below.

EQ-5D-5L index utility values were also derived by health state for use within the model, using a generalised estimating equations (GEE) regression analysis. Further details of this process are presented in Section B.3.4.5.

Table 51: EQ-5D-5L index values at baseline and follow-up assessments for the pooled population of NATALEE (ITT population)

Visit	N	Mean	SD
Screening	[redacted]	[redacted]	[redacted]
Visit 4	[redacted]	[redacted]	[redacted]
Visit 7	[redacted]	[redacted]	[redacted]
Visit 8	[redacted]	[redacted]	[redacted]
Visit 9	[redacted]	[redacted]	[redacted]

Visit	N	Mean	SD
Visit 10	[redacted]	[redacted]	[redacted]
Visit 11	[redacted]	[redacted]	[redacted]
Visit 12	[redacted]	[redacted]	[redacted]
Visit 13	[redacted]	[redacted]	[redacted]
Visit 15	[redacted]	[redacted]	[redacted]
Visit 17	[redacted]	[redacted]	[redacted]
Visit 19	[redacted]	[redacted]	[redacted]
Visit 21	[redacted]	[redacted]	[redacted]
Visit 23	[redacted]	[redacted]	[redacted]
Visit 25	[redacted]	[redacted]	[redacted]
End of treatment	[redacted]	[redacted]	[redacted]
Follow-up	[redacted]	[redacted]	[redacted]
Disease recurrence	[redacted]	[redacted]	[redacted]

Footnotes: In addition to the scheduled visits shown above, there were also 412 unscheduled visits. Assessments at follow-up visits occurred after the end of treatment visit. These visits would be after disease recurrence for patients who discontinued treatment due to recurrence. However, follow-up visits may occur before disease recurrence for patients who discontinued treatment for reasons other than recurrence. EQ-5D-5L index values from the ITT population of NATALEE are used across all economic analyses.
Abbreviation: EQ-5D-5L; EuroQol 5-Dimension 5-Level; ITT: intention-to-treat; SD: standard deviation.

B.3.4.2 Mapping

No mapping was undertaken, other than the crosswalk of EQ-5D-5L to EQ-5D-3L described in Section B.3.4.5.

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

An SLR was conducted in April 2023 and subsequently updated in October 2023 and July 2024, to identify potential utility data for use in the economic model. Full details of the methodology of the utilities SLR, including the search strategy and the study selection process, are presented in Appendix H.

Across both the original SLR and the two SLR updates, a total of three records, reporting on two studies with relevant utilities data, were included. In addition, ten studies identified in the economic evaluation SLR were identified as reporting relevant utilities data. An overview of all 12 studies is provided in Table 52. The health-state utility values applied within the economic model are detailed in Section B.3.4.5. In terms of reported health-state utility values in the literature, the closest aligning study to the economic evaluation in this submission is TA810.[6] The health-state utility values for iDFS and remission were 0.782. The NMR health-state utility value was reported as 0.76.[6]

The disutility values applied within the economic model are detailed in Section B.3.4.4. In terms of the disutility values identified in the literature, four studies reported a disutility for diarrhoea, ranging from -0.046 to -0.1198. The value used in the model (-0.103) is therefore within this range. Three studies reported disutility values for leukopenia, with a range of -0.003 to -0.009. The value used in the model of (-0.003) represents the lower end of the range. Four studies reported disutility values for lymphopenia, with a range of -0.087 to -0.09, and are close to the modelled value of -0.09. Three studies reported disutility values for neutropenia, with a range of -0.007 to -0.24. The modelled value of -0.007 represents the lower end of this range. Only one

study (TA810)[6] provided a disutility value for alanine aminotransferase increased, and was adopted within the economic model.

Table 52: Summary of studies reporting utility values identified in the SLRs

No.	Study	Country	Results	Increment/decrement in baseline utility
1.	Criscitiello *et al.* (2021)[144]	Multiple	EQ-5D, mean: • Global: 0.868; USA: 0.844; Japan: 0.842; France: 0.916; Germany: 0.845; Italy: 0.871; Spain: 0.867; UK: 0.872 • Stage I: 0.879; Stage II: 0.874; Stage III: 0.841	NR
2.	Rider *et al.* (2021)[145]	US, Germany and UK	EQ-5D, mean: • Not working: 0.73 • Working - WPAI <20: 0.915 • Working - WPAI 20-49: 0.841 • Working - WPAI ≥50: 0.754	NR
3.	Chang *et al.* (2022)[120]	USA	• EBC-stable: 0.86 • EBC-progressed: 0.767 • MBC-stable: 0.54 • MBC-progressed: 0.443 • Death: 0	• Diarrhoea: -0.1198 • Constipation: -0.0056 • Vomiting: -0.04802 • Alopecia: -0.0891 • Nausea: -0.1214 • Rash: -0.03248 • Neutropenia: -0.2466 • Anaemia: -0.1914 • Thrombocytopenia: -0.108 • Urinary tract infection: -0.2303 • Venous thromboembolic event: -0.1
4.	Fariman *et al.* (2024)[124]	USA	• No recurrence (1 year after primary BC diagnosis): 0.696 (range: 0.682–0.710) • No recurrence (subsequent years): 0.865 (range: 0.74–0.980) • BC recurrence: 0.67 (range: 0.53–0.870)	• Thromboembolism (applied for 1 cycle): −0.056 (range: −0.0678 to −0.0442) • Endometrial cancer (applied for 1 cycle): −0.036 (range: −0.0431 to −0.0289)
5.	Jongbloed *et al.* (2023)[118]	Netherlands	Standard treatment: • Recurrence-free: 0.87 (0.16)	Standard treatment: • Neutropenia: −0.087 (0.0087)

No.	Study	Country	Results	Increment/decrement in baseline utility
			• Recurrent disease: 0.87 (0.16) Additional abemaciclib: • Recurrence-free: 0.74 (0.26) • Recurrent disease: 0.74 (0.26)	• Leukopenia: −0.087 (0.0087) • Diarrhoea: −0.046 (0.0046) • Lymphopenia: −0.090 (0.009) Additional abemaciclib: • Neutropenia: −0.087 (0.0087) • Leukopenia: −0.087 (0.0087) • Diarrhoea: −0.046 (0.0046) • Lymphopenia: −0.090 (0.009)
6.	Wei *et al.* (2023)[125]	China	• iDFS: 0.965 (range: 0.744–0.980) • Nonmetastatic: 0.766 (range: 0.725–0.780) • Remission: 0.85 (range: 0.7–0.850) • Distant metastases: 0.642 (range: 0.615–0.690)	• Diarrhoea: −0.103 (range: 0.124–0.082) • Neutropenia: −0.09 (range: 0.108–0.072) • Lymphopenia: −0.09 (range: 0.108–0.072)
7.	Zhong *et al.* (2024)[123]	China	• First year of treatment: 0.81 (range: 0.648–0.972) • Primary and recurrent BC (second year): 0.9 (range: 0.720–1) • BC recurrence within 1 year: 0.779 (range: 0.623–0.934) • Metastatic cancer: 0.737 (range: 0.589–0.884) • Second cancer: 0.839 (range: 0.671–1) • Health utility of AE reduction - Thrombosis or embolism: 0.067 (range: 0.053–0.080) • Health utility of AE reduction - Fractures: 0.131 (range: 0.104–0.157)	NR
8.	Sra *et al.* (2024)[126]	India	• Disease-free: 0.87 (range: 0.957–0.783) • Locoregional recurrence: 0.61 (range: 0.668–0.547) • Metastases: 0.56 (range: 0.612–0.500)	• Diarrhoea: −0.046 (range: −0.051 to −0.041) • Neutropenia: −0.087 (range: −0.096 to −0.078) • Leukopenia: −0.09 (range: −0.099 to −0.081) • Lymphopenia: −0.09 (range: −0.099 to −0.081)

No.	Study	Country	Results	Increment/decrement in baseline utility
				• Pulmonary embolism: −0.475 (range: −0.523 to −0.428) • Interstitial lung disease: −0.409 (range: −0.45 to −0.368) • Liver-associated: −0.087 (range: −0.096 to −0.078)
9.	Galactionova *et al.* (2022)[132]	Global (Germany, Spain, USA, France, Australia, South Korea, Ireland, Japan, Austria, and the UK)	Global • Palbociclib + ET: 0.90 (0.13) • ET alone: 0.89 (0.14) Germany • Palbociclib + ET: 0.91 (0.12) • ET alone: 0.90 (0.12)	NR
10.	TA810[6]	UK	• iDFS health state: 0.782 • NMR health state: 0.76	iDFS health state • Neutropenia: -0.007 • Leukopenia: -0.003 • Diarrhoea: -0.103 • Fatigue: -0.003 • Alanine aminotransferase increase: -0.005 • Anemia: -0.119 • Abdominal pain: -0.048 • Lymphopenia: 0 • Aspartate aminotransferase increase: 0 • Thrombocytopenia: 0 • Venus thromboembolic event: 0 Metastatic recurrence health state • Dyspnoea: -0.029

No.	Study	Country	Results	Increment/decrement in baseline utility
				• Hyperglycaemia: -0.119 • Stomatitis: -0.269 • GGT increase: 0
11.	PBAC 2022[128]	Australia	• iDFS and remission: 0.783 • ER-MBC PFS and ES-MBC PFS2: 0.748[a] • ER-MBC PFS1: 0.724[b]	NR
12.	PBAC 2023[146]	Australia	• iDFS and remission: 0.785 • ER-MBC PFS and ES-MBC PFS2: 0.748[a] • ER-MBC PFS1: 0.724[b]	NR

Footnotes: [a] PFS2: Utility value for PFS health state from MONARCH-2 clinical trial; [b] PFS1: Utility value for PFS health state from MONARCH-3 clinical trial.
Abbreviations: AE: adverse event; BC: breast cancer; EBC: early breast cancer; ER: endocrine resistant; ES: endocrine sensitive; ET: endocrine therapy; GGT: gamma-glutamyl transferase; HRQoL: health-related quality of life; HR: Hormone receptor; HER2: Human epidermal growth factor receptor 2; iDFS: invasive disease-free survival; MBC: metastatic breast cancer; NMR: non metastatic recurrence; NR: not reported; PBAC: Pharmaceutical Benefits Advisory Committee; PFS: progression free survival; WPAI: work productivity and activity impairment.

B.3.4.4 Adverse reactions

For patients receiving ET in all four economic analyses, the mean health-state utility values for on-treatment iDFS generated from the AI arm of NATALEE were assumed to capture the effects of AEs on HRQoL. As such, no other adjustments for AE disutilities were included for ET to avoid double-counting.

For ribociclib plus AI in all four economic analyses, to compensate for the differences in AEs between ET and ribociclib plus AI, a QALY decrement was applied based on estimates of disutilities associated with each AE included in the model, differences in the incidence of AEs between ET and ribociclib plus AI, and the expected duration of each AE. The same approach was adopted for abemaciclib plus ET in Population 4 (node-positive high-risk eligible for abemaciclib).

The AE disutilities (per day) included for AEs associated with ribociclib plus AI across all four economic analyses as well as for abemaciclib plus ET in Population 4 (node-positive high-risk eligible for abemaciclib) are summarised below in Table 53. The disutilities for each AE were based on those used to inform decision making in TA810,[6] which were derived from NICE evaluations and values from the literature. The duration of all AEs (and therefore the duration of the disutility application) was based on those used to inform decision making in TA810,[6] which were derived from previous NICE evaluations and values from the literature.

Table 53: Disutility values for AEs included in all four economic analyses

AE	Disutility (per day)	Source	Mean duration (days)	Source
Alanine aminotransferase increased	-0.005	TA503[147] and TA810[6]	28.00	TA503[147] and TA810[6]
Diarrhoea	-0.103	TA612[148] and TA810[6]	8.00	TA612[148] and TA810[6]
Leukopenia	-0.003	Hudgens *et al.* (2016),[149] TA306,[150] TA579[151] and TA810[6]	13.96	TA306,[150] TA579[151] and TA810[6]
Lymphopenia	-0.007	Assumed to be the same as neutropenia	34.00	TA306[150] and TA810[6]
Neutropenia	-0.007	Hudgens *et al.* (2016),[149] TA306,[150] TA579[151] and TA810[6]	15.09	Nafees *et al.* (2008),[152] TA306,[150] TA579[151] and TA810[6]

Abbreviations: AE: adverse event; TA: technology appraisal.

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

Given the NATALEE trial collected EQ-5D-5L data from large numbers of patients that could be classified into health states that align with the economic model structure, the health state utility values used for all four economic analyses were derived directly from data collected within the ITT population of the NATALEE trial (April 2024 data cut).

The following section describes how the health state utility values adopted in all four economic

analyses were derived.

iDFS and NMR health state utility values

EQ-5D-5L assessment data from the April 2024 data cut of NATALEE were categorised by health state based on recorded event times and types for iDFS and OS; for the iDFS state only, assessments were further classified by patients on- and off-treatment. Numbers of patients as well as numbers of valid utility assessments were reported by time since the screening visit, as well as by health state (i.e., each patient could contribute multiple assessments to a given health state). The numbers of patients and EQ-5D-5L assessments by health state in the ITT population of NATALEE (from which health-state utility values for all four economic analyses were derived), are shown below in Table 54.

Table 54: Numbers of patients and assessments contributing to GEE regression analyses of EQ-5D-5L assessments for patients in NATALEE (ITT population)

Health state	Assessments	Patients
iDFS, ribociclib plus AI arm	[redacted]	[redacted]
iDFS, ET arm	[redacted]	[redacted]
iDFS on-treatment, ribociclib plus AI arm	[redacted]	[redacted]
iDFS on-treatment, ET arm	[redacted]	[redacted]
iDFS off-treatment	[redacted]	[redacted]
Post-recurrence (i.e., any reason)	[redacted]	[redacted]
Secondary primary malignancy	[redacted]	[redacted]
Non-metastatic recurrence	[redacted]	[redacted]
Distant recurrence	[redacted]	[redacted]

Abbreviations: AI: aromatase inhibitor; GEE: generalised linear model; iDFS: invasive disease-free survival; ITT: intention-to-treat; ET: endocrine therapy; EQ-5D-5L: EuroQol 5-Dimensions 5-Levels.
Source: Novartis Data on File (NATALEE Clinical Study Report April 2024 Data Cut).[79]

In accordance with the NICE position statement on the use of EQ-5D-5L to derive utility values, the EQ-5D-5L descriptive scores from NATALEE were mapped onto the EQ-5D-3L UK value set using the mapping function developed by Hernández Alava *et al.* (2017) through the NICE Decision Support Unit (DSU), using the Policy Research Unit in Economic Methods of Evaluation of Health and Care Interventions (EEPRU) dataset (Hernández Alava *et al.* [2020]).[153-155]

The EQ-5D data were analysed using generalised estimating equations (GEEs; an extension of generalised linear model [GLM] regression for analysing data with correlation of the dependent variable across observations) in order to obtain health state utility values that controlled for baseline EQ-5D. Patients could contribute multiple observations to the analysis and to be included in the analysis, patients had to have a baseline assessment and at least one post-baseline assessment.

Covariates used in the regressions were selected to correspond to health states in the economic model, as follows:

- iDFS on-treatment with ribociclib plus AI
- iDFS on-treatment with ET
- iDFS off-treatment

- NMR
- SPM
- DR

GEE regressions were then conducted using the SAS PROC GENMOD procedure with the REPEATED statement. An autoregressive correlation structure was chosen based on assessment of the Quasi-likelihood independence model criterion (QIC), consistent with the approach outlined in Cui and Qian (2007).[156]

Four different models were considered with different combinations of covariates (Table 55). Model 1 included an intercept term and a covariate for baseline utility value, a covariate for assessments post-disease recurrence, and a covariate for treatment arm. Models 2 and 4 included an additional covariate for on-treatment (i.e., as opposed to off-treatment) in iDFS. Models 3 and 4 included additional covariates controlling for type of recurrence (i.e., SPM, NMR, and DR).

Table 55: Regression models for analysing health-state utility values in NATALEE

Model	Intercept	Baseline Utility	iDFS (ribociclib plus AI)	iDFS (ET)[a]	iDFS off-treatment	iDFS on-treatment (ribociclib plus	iDFS on-treatment (ET)[a]	Post-recurrence	NMR	SPM	DR
1	√	√	√	√				√			
2	√	√			√	√	√	√			
3	√	√	√	√	√				√	√	√
4	√	√			√	√	√		√	√	√

Footnotes: [a] The AI arm of the NATALEE trial was used to inform the efficacy of ET, with an adjustment to account for the efficacy of tamoxifen.
Abbreviations: AI: aromatase inhibitor; ET: endocrine therapy; DR: distant recurrence; iDFS: invasive disease-free survival; NMR: non-metastatic recurrence; SPM: secondary primary malignancy.

Coefficients and mean utility estimates based on the four regression models are presented in Appendix T.

Whilst Model 1 had the best fit based on QIC (see Appendix T.1) this model did not include covariates for each type of recurrence (i.e., it assumed the same utility value for SPM, non-metastatic, and distant recurrences). It was therefore preferred to use a regression model that provided separate utility estimates for each of the mutually exclusive health states in the economic model structure. As such, Model 4 was chosen for use within the model. A summary of the health state utility values for iDFS (on- and off-treatment) and NMR, derived from GEE Model 4 are presented below in Table 56.

Remission and DR health states

The health-state utility value for patients in remission was assumed to be the same as for iDFS off-treatment, in line with the assumption made in TA810.[6]

As for iDFS and NMR, the health-state utility value for the PFS substates of the DR ET-resistant

and ET-sensitive health states were estimated from NATALEE (April 2024 data cut).[79]

For the PPS substates of the DR ET-resistant and ET-sensitive health states, information regarding subsequent progressions after advanced or metastatic recurrence was not captured in NATALEE, therefore it was not possible to estimate EQ-5D-derived health state utility values for these substates from NATALEE. Therefore, utility values for the PPS states of each DR substate were calculated by taking the ratio of the health state utility values estimated for the PFS and PPS health states for the previous NICE evaluations of ribociclib based on MONALEESA-2 and MONALEESA-3, and applying that ratio of the health state utility value for the DR PFS substate estimated from NATALEE.[157, 158] These decreases were as follows; [redacted] for ET-resistant ([redacted]), and [redacted] for ET-sensitive ([redacted]).

Utility values used in the economic analysis

The health-state utility values derived from the ITT population of NATALEE are presented below in Table 56. The utility values derived for ET were chosen as the referent group as ET has a lower AE profile than ribociclib plus AI. Disutilities were then applied to the ribociclib plus AI arm (Populations 1–4) and the abemaciclib plus ET arm (Population 4 only) as described in Section B.3.4.4. Scenario analyses were conducted for all four populations using the utility values utilised in TA810.[6]

Table 56: Health-state utility values adopted in all four economic analyses

Health state	Utility estimate	SE	95% CI	No. of visits	No. of patients	Source
On-treatment iDFS	0.7620	[redacted]	[redacted]	[redacted]	[redacted]	NATALEE April 2024 data cut[79]
Off-treatment iDFS	0.7367	[redacted]	[redacted]	[redacted]	[redacted]	NATALEE April 2024 data cut[79]
Remission	0.7367	[redacted]	[redacted]	-	-	Assumed equal to health state utility value for iDFS off-treatment, based on assumption made in TA810[6]
NMR	0.6818	[redacted]	[redacted]	[redacted]	[redacted]	NATALEE April 2024 data cut[79]
DR[a]	0.6190	[redacted]	[redacted]	[redacted]	[redacted]	NATALEE April 2024 data cut[79]
ET-resistant DR PFS	0.6190	-	-	-	-	NATALEE April 2024 data cut and assumed equal utility between ET-resistant and ET-sensitive substates[79]
ET-resistant DR PPS	0.5755	-	-	-	-	Calculated by taking the ratio of the utility values estimated for the PFS and PPS health states of the previous ribociclib evaluations based on MONALEESA-2 and MONALEESA-3,[87, 133] and applying that ratio of the utility value for the DR PFS state estimated from the NATALEE April 2024 data cut[79]
ET-sensitive DR PFS	0.6190	-	-	-	-	NATALEE April 2024 data cut and assumed equal utility between ET-resistant and ET-sensitive substates[79]
ET-sensitive DR PPS	0.5944	-	-	-	-	Calculated by taking the ratio of the utility values estimated for the PFS and PPS health states of the previous ribociclib evaluations based on MONALEESA-2 and MONALEESA-3, and applying that ratio of the utility value for the DR PFS state estimated from the NATALEE April 2024 data cut[79]

Footnotes: [a] Health state utility value not used directly in the model, but ET-resistant and ET-sensitive DR PFS health state utility values were assumed to equal the health state utility value for DR derived from the NATALEE trial (April 2024 data cut).
Abbreviations: CI: confidence interval; DR: distant recurrence; ET: endocrine therapy; iDFS: invasive disease-free survival; NMR: non metastatic occurrence; PFS: progression-free survival; PPS: post-progression survival; SE: standard error.

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

An SLR was conducted in April 2023, and subsequently updated in October 2023 and July 2024 to identify cost and resource use studies conducted in patients with HR+/HER2– EBC. Full details are presented in Appendix I.

Overall, 16 included studies (reported on by 18 records) reported data pertaining to healthcare costs among patients with HR+/HER2− EBC. Of these, seven studies were conducted in the US, three were conducted in Italy, and one study each was conducted in Canada, Germany the UK, Portugal, New Zealand and multiple countries (Table 57).

Given the availability of direct healthcare unit costs from the British National Formulary (BNF), the electronic Market Information Tool (eMIT) and NHS reference costs, no costs from the SLR were utilised within the economic model. Details of the costs utilised within the economic analyses are presented in the following sections.

Table 57: Summary of studies reporting costs identified in the SLR

Study Name	Patient population	Country	Sample size	Intervention/ comparator	Outcomes reported
Vitko *et al.* (2024)[159]	HR+/HER2–, node-positive EBC patients at high risk of recurrence	US	3,081	-	Drug costs, all HCRU costs related to treatment
Dell'Anno *et al.* (2023)[160]	HR+/HER2− BC	Italy	Cohort A (n=2,019) Cohort B (n=420) Cohort C (n=164)	-	Drug costs, HCRU costs (hospitalisation cost, outpatient specialist care costs)
Earla *et al.* (2024)[161]	HR+/HER2− EBC patients	US	25,899	-	HCRU costs (inpatient admissions, ED visits, outpatient visits, SNF stays, other visits.)
Wu *et al.* (2024)[162]	HR+/HER2− Stage I BC (⩾ 70 years of age with node-negative disease)	US	-	Anti-oestrogen therapy vs 5-fraction radiation therapy alone; ET plus 5-fraction radiation therapy; 15-fraction radiation therapy alone; ET plus 15-fraction	Drug costs

Study Name	Patient population	Country	Sample size	Intervention/ comparator	Outcomes reported
				radiation therapy	
INAHTA/G-BA 2022[107]	HR+/HER2− EBC patients at high risk of recurrence (premenopausal women, postmenopausal women, and men)	Germany	-	-	Drug costs
Lao *et al.* (2022)[163]	ER+/HER2– EBC patients	New Zealand	15,615	-	Drug costs, HCRU costs (outpatient services, inpatient services, diagnostic and monitoring costs)
Valsecchi *et al.* (2022)[164]	HR+/HER2– EBC patients	Italy	31,863	-	HCRU (breakdown of patients receiving adjuvant CT and ET)
Berdunov *et al.* (2021)[165]	HR+/HER2– EBC patients	UK	-	-	Drug costs, administration costs, AE costs, HCRU costs associated with recurrence
Brezden-Masley *et al.* (2021)[166]	Invasive HR+/HER2– EBC patients	Canada	21,360	-	Drug costs, HCRU costs (ambulatory cancer professional, inpatient services, outpatient services, home care, surgery, diagnostics)
Brandão *et al.* (2020)[167]	HR+/HER2– EBC patients	Portugal	537	-	HCRU costs (appointments, hospitalisation, genetic testing, imaging, other medical expenses)
Calip *et al.* (2020)[168]	HR+/HER2– EBC patients	US	889	-	HCRU costs (doctor/ specialist visits, routine care visits, hospitalisations,

Study Name	Patient population	Country	Sample size	Intervention/ comparator	Outcomes reported
					prescription medication)
Vaz-Luis *et al.* (2015)[169]	HR+/HER2– EBC patients	US	6,792	-	HCRU costs (Proportion of patients using CT, breakdown of CT treatment type by cancer stage)
NATALEE trial[28]	HR+/HER2– EBC patients	International	5,101	Ribociclib plus ET vs ET	HCRU costs (hospitalisations, hospital LoS, AE)
Zheng *et al.* (2023)[170]	Women aged ≥66 years old at diagnosis, Stage I-III HR+ BC	US	25,796[a]	Hormone therapy	Drug costs, HCRU costs (hospitalisations, hospital LoS, ED visits, inpatient services, outpatient services, appointments)
Perrone *et al.* (2023)[171]	Adult (≥18 years old) female patients with BC	Italy	24,137	ET plus CT	Drug costs, HCRU costs (hospitalisations, medical tests)
Berdunov *et al.* (2022)[172]	HR+/HER2– EBC patients	US	-	CET vs ET	Drug costs (administration, AE costs)

Footnotes: [a] 21,082 (>80%) patients were HR+/HER2–.
Abbreviations: AE: adverse event; BC: breast cancer; CET: combined chemo-endocrine therapy; CT: chemotherapy; EBC: early breast cancer; ED: emergency department; ET: endocrine therapy; G-BA: Gemeinsamer Bundesausschuss; HCRU: healthcare-resource utilisation; HER2; human epidermal growth factor receptor 2; HR: hormone receptor; INAHTA: International Network of Agencies for Health Technology Assessment; LoS: length of stay; SLR: systematic literature review; UK: United Kingdom; US: United States.

B.3.5.1 Intervention and comparator drug acquisition costs

Drug acquisition costs for the intervention, comparators, and subsequent therapies included in the economic analyses were calculated based on the dosing regimens from the respective SmPCs of each therapy.

The drug acquisition cost for ribociclib (as both the intervention and as a subsequent therapy) was included in the economic analyses at PAS price. All drug acquisition costs for the comparators and subsequent therapies were included in the economic analyses at list price (with the exception of alpelisib which, as a Novartis drug, was included at PAS price) and were sourced from the BNF and eMIT.

Drug acquisition costs: intervention and comparators

Ribociclib plus AI

Across all four economic analyses, the drug acquisition costs of ribociclib were calculated based on the anticipated licensed dosing regimen and the dosing regimen used in NATALEE.[1, 2] This is

400 mg (two 200 mg film-coated tablets) administered orally once daily for 21 consecutive days followed by seven days off treatment, resulting in a complete treatment cycle of 28 days.

A relative dosing intensity (RDI) of [redacted] for ribociclib was also applied, derived from the ITT population of the NATALEE trial (April 2024 data cut]).[79] The cost of ribociclib is priced linearly, such that the cost per mg remains the same between packages of different dose amounts. Cost reductions for ribociclib (for permitted dose reductions, from 400 mg to 200 mg in the case of potential toxicities) were therefore assumed to be fully captured in the RDI, which counts these dose reductions as being below the planned dose.

The RDI and overall drug acquisition cost per cycle for ribociclib within the model were the same for all four economic analyses as they are not expected to differ by population. Duration of treatment with ribociclib does differ between populations, based on TTD data as described in Section B.3.3.3.

The drug acquisition costs for AI (as part of ribociclib plus AI) were calculated as a basket of all AI therapies available in UK clinical practice, informed by UK clinical experts (see Appendix Q.3). These included the following:

- Letrozole 2.5 mg administered orally once daily
- Anastrozole 1 mg administered orally once daily
- Exemestane 25 mg administered orally once daily
- Goserelin 3.6 mg administered subcutaneously once every 28 days
- Zoledronic acid 4 mg administered orally once every 6 months

The treatment mix of AIs within the AI therapy basket was based on the NATALEE trial (ITT population) and adjusted based on UK clinical expert feedback obtained at an advisory board in September 2024 (see Appendix Q.3). Different estimates were obtained for patients in Population 1 (NATALEE ITT) and Population 4 (node-positive high-risk eligible for abemaciclib). The treatment mix of AIs within the AI therapy basket in Populations 2 and 3 was assumed to be the same as the treatment mix used in Population 1.

For the proportion of patients estimated to receive goserelin as part of ribociclib plus AI, clinical experts at the September 2024 advisory board noted that the observed goserelin usage of [redacted] in the NATALEE trial (ITT population) was high, and instead should align to the proportion of premenopausal patients expected to present in UK clinical practice (see Appendix Q.3). As such, the study by Tarantino *et al*. (2024) was used to estimate the proportion of premenopausal patients among patients in Population 1 (NATALEE ITT; 24.4%) and patients in Population 4 (node-positive high-risk eligible for abemaciclib; 26.0%).[7] However, as menopausal status was unknown for ~13% of patients in the study by Tarantino *et al.* (2024),[7] estimates for the proportion of premenopausal and postmenopausal patients were inflated to sum to 100%. The resulting estimates for goserelin usage among patients receiving ribociclib plus AI in the base case (Population 1 [NATALEE ITT]) was [redacted] and in Population 4 (node-positive high-risk eligible for abemaciclib), for ribociclib plus AI and for abemaciclib plus ET, was [redacted]. As for the AI therapy treatment mix, the proportion of patents estimated to receive goserelin alongside ribociclib plus AI in Populations 2 and 3 was assumed to be the same as in Population 1.

Finally, the proportion of patients receiving zoledronic acid was based on the proportion of

patients in NATALEE (ITT population) who received a bisphosphonate, and applied across all four economic analyses.

In Population 1, RDIs were applied for anastrozole ([redacted]), letrozole ([redacted]) and goserelin ([redacted]), derived from the ribociclib plus AI arm for the ITT population in the NATALEE trial (April 2024 data cut).[79] In the absence of RDI data for exemestane, this was assumed to be the same as for anastrozole and letrozole ([redacted]). In the absence of RDI data for zoledronic acid, this was assumed to be [redacted] For Populations 2–4, the same RDIs for AI (as part of ribociclib plus AI) were assumed as per Population 1. Scenario analyses were conducted across all four economic analyses whereby the RDIs for all ETs (as monotherapy and in combination with ribociclib or abemaciclib [Population 4 only]), goserelin and zoledronic acid, were assumed to be [redacted].

Full details of the drug acquisition costs assumed for ribociclib plus AI in the model are presented in Table 58. Drug administration costs are described in detail in Section B.3.5.3.

ET

As for the AI therapies above, the drug acquisition costs of the ET comparator were calculated as a basket of all ETs available in UK clinical practice, informed by UK clinical experts (see Appendix Q.3). These included the following:

- Tamoxifen 20 mg administered orally once daily
- Letrozole 2.5 mg administered orally once daily
- Anastrozole 1 mg administered orally once daily
- Exemestane 25 mg administered orally once daily
- Goserelin 3.6 mg administered subcutaneously on day 1 of a 28-day cycle
- Zoledronic acid 4 mg administered orally on day 1 of a 183-day cycle

The treatment mix of ETs within the ET basket was based on the NATALEE trial (ITT population), with the addition of exemestane and tamoxifen, and adjusted based on UK clinical expert feedback obtained at an advisory board in September 2024 (see Appendix Q.3). Different estimates were obtained for patients in Population 1 (NATALEE ITT) and Population 4 (node-positive high-risk eligible for abemaciclib). The treatment mix of ETs within the ET therapy basket in Populations 2 and 3 was assumed to be the same as the treatment mix used in Population 1.

The proportion of patients receiving zoledronic acid was based on the proportion of patients in NATALEE (ITT population) who received a bisphosphonate and applied across all four economic analyses.

In Population 1, RDIs were applied for anastrozole ([redacted]), letrozole ([redacted]) and goserelin ([redacted]), derived from the AI arm for the ITT population in the NATALEE trial (April 2024 data cut).[79] In the absence of RDI data for exemestane, this was assumed to be the same as for anastrozole and letrozole ([redacted]). In the absence of RDI data for tamoxifen and zoledronic acid, this was assumed to be [redacted] For Populations 2–4, the same RDIs for ET were assumed as per Population 1. As mentioned above, scenario analyses were conducted across all four economic analyses whereby the RDIs for all ETs (as monotherapy and in combination with ribociclib or abemaciclib [Population 4 only]), goserelin and zoledronic acid, were assumed to be [redacted].

Full details of the drug acquisition costs assumed for ET in the model are presented in Table 58.

Drug administration costs are described in detail in Section B.3.5.3.

Abemaciclib plus ET

The drug acquisition costs of abemaciclib in Population 4 (node-positive high-risk eligible for abemaciclib) were calculated based on the licensed dosing regimen and the dosing regimen used in monarchE.[77, 135] This is 300 mg administered orally daily (2 x 150 mg film-coated tablets twice daily).

In the absence of publicly available data for the RDI for abemaciclib (for Population 4 [node-positive high-risk eligible for abemaciclib]), the RDI for abemaciclib was based on the RDI for treatment holds (i.e., treatment pauses) for ribociclib in the NATALEE trial (ITT population; April 2024 data cut).[79] The RDI for treatment holds was used for abemaciclib since, due to flat pricing, cost savings would only be incurred for treatment holds and not for dose reductions. The RDI for treatment holds was calculated as the RDI for ribociclib divided by the average daily dose intensity, with the latter calculated as the average daily dose divided by the planned dose.

The study protocol in monarchE allowed for a maximum of two dose reductions for abemaciclib to manage AEs. The first dose reduction was from 150 mg twice daily (300 mg total) to 100 mg twice daily (200 mg total), and the second dose reduction was from 100 mg twice daily to 50 mg twice daily (100 mg total). Given abemaciclib treatment packs are associated with flat pricing, it was assumed that the cost associated with abemaciclib pack wastage would be accrued by 50% of patients who required down-dosing given that, on average, the down-dosing would occur halfway through the pack at the original dose being consumed. The proportion of patients requiring down-dosing with abemaciclib (single down-dose: 29.81%; two down-doses: 13.94%) was based on analyses of the monarchE trial reported by Goetz *et al.* (2024).[173]

The treatment mix of ETs (as part of abemaciclib plus ET) was based on UK clinical expert feedback obtained at an advisory board in September 2024 (see Appendix Q.3). RDIs for the ET components of abemaciclib plus ET were assumed to be 100%, based on TA810.[6] In the absence of any other estimate, the RDIs for goserelin and zoledronic acid were set to [redacted]

Scenario analyses were conducted across all four populations whereby the RDIs for all ETs (as monotherapy and in combination with ribociclib or abemaciclib [Population 4 only]), in addition to goserelin, were assumed to be [redacted]. A further scenario analysis was conducted in Population 4 (node-positive high-risk eligible for abemaciclib) whereby the RDI for abemaciclib was assumed equal to the RDI for ribociclib ([redacted] and the RDIs for ET (in combination with abemaciclib) were assumed to be equal to the RDIs for the relevant AIs in combination in ribociclib. In the latter scenario analysis, the RDIs for tamoxifen and zoledronic acid were set to [redacted]

Full details of the drug acquisition costs assumed for abemaciclib plus ET in the model are presented in Table 58. Drug administration costs are described in detail in Section B.3.5.3.

Maximum treatment durations

Across all four economic analyses, a maximum treatment duration was applied for AI and ribociclib according to the NATALEE trial design:[2]

- For AI (as part of ribociclib plus AI) and for ET, a maximum duration of five years was applied. Feedback from UK clinical experts is that for some patients, treatment with AI/ET may continue for up to 10 years (see Appendix Q.2); as such, two scenario analyses were

conducted whereby the maximum treatment duration for AI (as part of ribociclib plus AI) and for ET was set to 7 years and 10 years, respectively.

- For ribociclib, a maximum treatment duration of 3 years was applied, in line with the expected prescribing in UK clinical practice and per the NATALEE trial.[22]

For the subgroup economic analysis in Population 4 (node-positive high-risk eligible for abemaciclib), a maximum treatment duration of 2 years was applied to abemaciclib, in line with the expected prescribing in UK clinical practice and per the maximum treatment duration in the monarchE trial.[45]

Table 58: Intervention and comparator drug acquisition and administration costs included the economic analysis

	Regimen	Drug	Method of administration	Daily dose (mg)	Days dosed per treatment cycle	Days per treatment cycle	Max treatment cycles	RDI	Percent receiving	Drug cost per dose (£)	Admin cost per model cycle (£)	Drug acquisition cost per model cycle (£)
Populations 1–3 (NATALEE ITT; node-positive high-risk; node-negative high-risk)	**Ribociclib plus AI**	Ribociclib	Oral	400	21	28	39.13	[redacted]	[redacted]	[redacted]	0.00	[redacted]
		Letrozole	Oral	2.5	30	30	60.88	[redacted]	[redacted]	0.03	0.00	0.60
		Anastrozole	Oral	1	30	30	60.88	[redacted]	[redacted]	0.02	0.00	0.07
		Exemestane	Oral	25	30	30	60.88	[redacted]	[redacted]	0.14	0.00	0.58
		Goserelin	SC	3.6	1	28	65.22	[redacted]	[redacted]	70.00	13.16	19.87
		Zoledronic acid	IV	4	1	183	6.00	[redacted]	[redacted]	4.00	5.85	0.11
	ET	Tamoxifen	Oral	20	30	30	60.88	[redacted]	[redacted]	0.10	0.00	0.54
		Letrozole	Oral	2.5	30	30	60.88	[redacted]	[redacted]	0.03	0.00	0.51
		Anastrozole	Oral	1	30	30	60.88	[redacted]	[redacted]	0.02	0.00	0.05
		Exemestane	Oral	25	30	30	60.88	[redacted]	[redacted]	0.14	0.00	0.39
		Goserelin	SC	3.6	1	28	65.22	[redacted]	[redacted]	70.00	11.75	17.54
		Zoledronic acid	IV	4	1	183	6.00	[redacted]	[redacted]	4.00	6.08	0.11
Population 4 (node-positive	**Ribociclib plus AI**	Ribociclib	Oral	400	21	28	39.13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Letrozole	Oral	2.5	30	30	60.88	[redacted]	[redacted]	0.03	0.00	0.60

	Regimen	Drug	Method of administration	Daily dose (mg)	Days dosed per treatment cycle	Days per treatment cycle	Max treatment cycles	RDI	Percent receiving	Drug cost per dose (£)	Admin cost per model cycle (£)	Drug acquisition cost per model cycle (£)
high-risk eligible for abemaciclib)		Anastrozole	Oral	1	30	30	60.88	[redacted]	[redacted]	0.02	0.00	0.07
		Exemestane	Oral	25	30	30	60.88	[redacted]	[redacted]	0.14	0.00	0.58
		Goserelin	SC	3.6	1	28	65.22	[redacted]	[redacted]	70.00	14.10	21.29
		Zoledronic acid	IV	4	1	183	6.00	[redacted]	[redacted]	4.00	5.85	0.11
	Abemaciclib plus ET	Abemaciclib	Oral	300	30	30	24.35	[redacted]	[redacted]	105.36	0.00	2,691.29
		Tamoxifen	Oral	20	30	30	60.88	[redacted]	[redacted]	0.10	0.00	0.20
		Letrozole	Oral	2.5	30	30	60.88	[redacted]	[redacted]	0.03	0.00	0.56
		Anastrozole	Oral	1	30	30	60.88	[redacted]	[redacted]	0.02	0.00	0.07
		Exemestane	Oral	25	30	30	60.88	[redacted]	[redacted]	0.14	0.00	0.54
		Goserelin	SC	3.6	1	28	65.22	[redacted]	[redacted]	70.00	14.10	21.00
		Zoledronic acid	IV	4	1	183	6.00	[redacted]	[redacted]	4.00	5.85	0.11
	ET	Tamoxifen	Oral	20	30	30	60.88	[redacted]	[redacted]	0.10	0.00	0.27
		Letrozole	Oral	2.5	30	30	60.88	[redacted]	[redacted]	0.03	0.00	0.56
		Anastrozole	Oral	1	30	30	60.88	[redacted]	[redacted]	0.02	0.00	0.06

	Regimen	Drug	Method of administration	Daily dose (mg)	Days dosed per treatment cycle	Days per treatment cycle	Max treatment cycles	RDI	Percent receiving	Drug cost per dose (£)	Admin cost per model cycle (£)	Drug acquisition cost per model cycle (£)
		Exemestane	Oral	25	30	30	60.88	[redacted]	[redacted]	0.14	0.00	0.49
		Goserelin	SC	3.6	1	28	65.22	[redacted]	[redacted]	70.00	14.10	21.04
		Zoledronic acid	IV	4	1	183	6.00	[redacted]	[redacted]	4.00	6.08	0.11

Footnote: [a]Drug acquisition cost for ribociclib incorporates the confidential PAS.
Abbreviations: AI: aromatase inhibitor; ET: endocrine therapy; IV: intravenous; ITT: intention-to-treat; PAS: patient access scheme; RDI: relative dose intensity; SC: subcutaneous.

B.3.5.2 Subsequent treatment drug acquisition costs

The economic analyses also included drug acquisition and administration costs for the therapies received following progression on initial treatment.

Patients entering the NMR state were assumed to receive ET (either letrozole, anastrozole, exemestane or tamoxifen). The same treatment mix of ET in the NMR health state was assumed across all four populations, aligned to the treatment mix utilised within the iDFS health state for Population 1 (NATALEE ITT; see Table 58). This is with the exception of zoledronic acid, which was not assumed to be received in the NMR health state, given its maximum treatment duration of 3 years, and in line with the approach taken in TA810.[6] Modelling the NMR treatment mix in line with the iDFS treatment mix was in line with the approach used to inform decision making in TA810.[6]

The proportions of patients receiving each subsequent therapy in the DR health states were based on UK clinical expert feedback received at the Company advisory board held in September 2024 (see Appendix Q.3). Feedback from UK clinical experts indicated that patients in the ET-sensitive DR health state might be retreated with CDK4/6 inhibitors, based on the recent changes to the NHS Blueteq for CDK4/6 inhibitors, which permits the retreatment of patients who received a CDK4/6 inhibitor in the adjuvant EBC-setting with a further CDK4/6 inhibitor provided the relapse occurred >12 months after completing adjuvant CDK4/6 inhibitor treatment.[174] As such, in the base case economic analysis, it was assumed that 45% of patients in the ribociclib plus AI arm of the model would receive retreatment with a CDK4/6 inhibitor in the ET-sensitive DR health state. This represents half of the proportion assumed to receive a CDK4/6 inhibitor in the ET-sensitive DR health state in the ET arm of the model (90%). The remaining 55% of patients in the ET-sensitive DR health state (ribociclib plus AI arm of the model) were assumed to receive chemotherapy with capecitabine. The same subsequent therapy treatment mixes were assumed across all four economic analyses.

Two scenario analyses were conducted across all four economic analyses to explore the impact of CDK4/6 inhibitor retreatment on the base case results whereby: 90% of patients in the ribociclib plus AI arm of the model would receive retreatment with a CDK4/6 inhibitor in the ET-sensitive DR health state (in line with the ET arm of the model); 70% of patients in the ribociclib plus AI arm of the model would receive retreatment with a CDK4/6 inhibitor in the ET-sensitive DR health state (with the remaining 30% receiving chemotherapy with capecitabine).

The proportions of patients assumed to receive each subsequent therapy by health state and treatment arm are presented in Table 59. The dosing regimens used to calculate the drug acquisition costs of the subsequent therapies within the economic analyses are summarised in Table 60. The dosing regimens and RDI for each subsequent therapy were based on the relevant clinical trials and/or SmPCs.[86, 133, 175-182]

Table 59: Treatment mix of subsequent therapies

Health state	Subsequent therapy	Proportion of patients receiving each subsequent therapy after treatment with:		
		Ribociclib plus AI (Populations 1–4)	ET (Populations 1–4)	Abemaciclib plus ET (Population 4 only)
NMR	Letrozole	[redacted]	[redacted]	[redacted]
	Anastrozole	[redacted]	[redacted]	[redacted]
	Exemestane	[redacted]	[redacted]	[redacted]
	Tamoxifen	[redacted]	[redacted]	[redacted]
	Goserelin	[redacted]	[redacted]	[redacted]
DR ET-sensitive	Ribociclib plus AI	[redacted]	[redacted]	[redacted]
	Palbociclib plus AI	[redacted]	[redacted]	[redacted]
	Abemaciclib plus AI	[redacted]	[redacted]	[redacted]
	Capecitabine	[redacted]	[redacted]	[redacted]
DR ET-resistant	Ribociclib plus fulvestrant	[redacted]	[redacted]	[redacted]
	Palbociclib plus fulvestrant	[redacted]	[redacted]	[redacted]
	Abemaciclib plus fulvestrant	[redacted]	[redacted]	[redacted]
	Everolimus plus exemestane	[redacted]	[redacted]	[redacted]
	Capecitabine	[redacted]	[redacted]	[redacted]
	Paclitaxel	[redacted]	[redacted]	[redacted]
	Alpelisib	[redacted]	[redacted]	[redacted]

Abbreviations: AI: aromatase inhibitor; DR: distant recurrence; ET: endocrine therapy; NMR: non-metastatic recurrence.

Table 60: Dosing schedules of subsequent therapies

Subsequent therapy	Drug	Daily dose	Basis of dose	Days dosed per treatment cycle	Days per treatment cycle	RDI	Source
Ribociclib plus fulvestrant	Ribociclib	600	mg/day	21	28	92.06%	MONALEESA-3[133, 183]
	Fulvestrant	500	mg/day	3	30	100.00%	
	Fulvestrant	500	mg/day	1	30	100.00%	
Palbociclib plus fulvestrant	Palbociclib	125	mg/day	21	28	89.80%	PALOMA3[175, 184]
	Fulvestrant	500	mg/day	3	30	100.00%	
	Fulvestrant	500	mg/day	1	30	100.00%	
Abemaciclib plus fulvestrant	Abemaciclib	300	mg/day	28	28	79.80%	MONARCH 2[176]
	Fulvestrant	500	mg/day	2	28	100.00%	
	Fulvestrant	500	mg/day	1	28	100.00%	
Everolimus plus exemestane	Everolimus	10	mg/day	28	28	86.00%	BOLERO-2[177]
	Exemestane	25	mg/day	28	28	100.00%	
Palbociclib plus AI	Palbociclib	125	mg/day	21	28	93.00%	PALOMA-1[178]
	Letrozole	2.5	mg/day	28	28	100.00%	
Ribociclib plus AI	Ribociclib	600	mg/day	21	28	87.50%	MONALEESA-2[87]
	Letrozole	2.5	mg/day	28	28	100.00%	
Abemaciclib plus AI	Abemaciclib	300	mg/day	28	28	86.00%	MONARCH 3[179]
	Anastrozole	1	mg/day	28	28	50.00%	
	Letrozole	2.5	mg/day	28	28	50.00%	
Exemestane	Exemestane	25	mg/day	28	28	100.00%	EFFECT[180]
Tamoxifen	Tamoxifen	20	mg/day	28	28	100.00%	Bachelot *et al.* (2012)[181]
Capecitabine	Capecitabine	2,500	per m^2	14	21	100.00%	Capecitabine SmPC[183]
Alpelisib plus fulvestrant	Alpelisib	300	mg/day	28	28	80.00%	Alpelisib SmPC[184]
	Fulvestrant	500	mg/day	3	30	100.00%	

Subsequent therapy	Drug	Daily dose	Basis of dose	Days dosed per treatment cycle	Days per treatment cycle	RDI	Source
	Fulvestrant	500	mg/day	1	30	100.00%	
Paclitaxel	Paclitaxel	260	mg/m^2	1	21	100.00%	Paclitaxel SmPC[185]

Abbreviations: AI: aromatase inhibitors; RDI: relative dose intensity.

The drug acquisition costs for each subsequent therapy are summarised in Table 61.

Table 61: Subsequent therapy drug acquisition costs included the economic analysis

Drug	List price per unit, package, or vial	Mg per capsule, tablet, or mL of solution	Method of administration	Source
Ribociclib	[redacted]	200	Oral	Novartis Data on File.
Abemaciclib	£2,950.00	150	Oral	BNF 2024, Abemaciclib, Verzenios 150mg tablets. Available at: https://bnf.nice.org.uk/drugs/abemaciclib-specialist-drug/medicinal-forms/
Exemestane	£4.20	25	Oral	eMIT 2023, Exemestane 25mg tablets / Packsize 30, DHC052
Palbociclib	£2,950.00	125	Oral	BNF 2024, Palbociclib, Ibrance 125mg tablets. Available at: https://bnf.nice.org.uk/drugs/palbociclib-specialist-drug/medicinal-forms/
Fulvestrant	£55.32	250	IM	eMIT 2023, Fulvestrant 250mg/5ml solution for injection pre-filled syringes / Packsize 2, DHC056
Everolimus	£488.32	10	Oral	eMIT 2023, Everolimus 10mg tablet (generic) / Packsize 30, DLK044
Capecitabine	£22.51	500	Oral	eMIT 2023, Capecitabine 500mg tablets / Packsize 120, DHA225
Alpelisib	[redacted]	150	Oral	Novartis Data on File.
Paclitaxel	£9.13	100	IV	eMIT 2023. Paclitaxel 100mg/16.7ml solution for infusion vials / Packsize 1, DHA145

Footnote: [a] Drug acquisition cost for ribociclib and alpelisib incorporates the confidential PAS.
Abbreviations: BNF: British National Formulary; eMIT: electronic market information tool; IM: intramuscular; Mg: milligrams; mL: millilitres; SC: subcutaneous.

Post-progression drug costs in the DR health state

Treatments received following progression on the subsequent therapies received in the DR health states were not explicitly modelled. Instead a monthly drug cost of £1,170.00 was applied to the PD substate of the DR health state, based on the mid-point of the Appraisal Committee's preferred assumptions in TA496 (the Appraisal Committee concluded that it would consider costs in the region of £1,140 to £1,200 in its decision making).[5]

B.3.5.3 Drug administration costs

For both the intervention and comparator therapies and the post-progression therapies, the cost of drug administration was incorporated into the economic analysis. The administration costs applied in the economic model have been detailed in Table 62 below. The same drug administration unit costs were adopted, where applicable, across all four economic analyses.

Table 62: Drug administration costs

Drug	Parameter	Category	Cost	Source
Intramuscular (IM)	Loading dose	**Total cost**	**£315.03**	**First administration plus second administration**
		First administration	£235.46	NHS Reference Costs 22-23; Outpatient Consultant Led Non-Admitted Face-to-Face Attendance, First [WF01B], Clinical Oncology Service.
		Second administration	*£79.58*	Weighted average of outpatient and primary care costs below
		Cost, outpatient	£144.83	NHS Reference Costs 22-23; Outpatient Consultant Led Non-Admitted Face-to-Face Attendance, Follow-up [WF01A], Clinical Oncology Service.
		Cost, primary care	£47.00	PSSRU 2023; unit cost per working hour for nurses, Band 5
		Proportion receiving outpatient	33%	Assumed equal to assumptions in TA687
		Proportion receiving primary care	67%	Assumed equal to assumptions in TA687
	Subsequent doses	**Total cost**	**£79.58**	Assumed equal to second administration cost of loading dose
	Input		**Cost**	**Source**
Subcutaneous (SC)	Cost of administration		£47.00	PSSRU 2023; unit cost per working hour for nurses, Band 5
	Cost of first administration		£217.22	NHS Reference Costs 22-23; Deliver Simple Parenteral Chemotherapy at First Attendance [SB12Z].

Intravenous (IV)	Cost of subsequent administrations	£249.23	NHS Reference Costs 22-23; Deliver Subsequent Elements of a Chemotherapy Cycle [SB15Z].
Oral	Cost of administration	£0.00	Assumption

Abbreviations: IM: intramuscular; IV: intravenous; NHS: National Health Service; SC: subcutaneous; PSSRU: Personal Social Services Research Unit.

B.3.5.4 Health state unit costs and resource use

Unit costs of follow-up and monitoring services by health state were based on data from NHS reference costs 2022/2023.[186] Follow-up and monitoring costs were considered separately for the iDFS, NMR, DR, and remission health states. The same follow-up and monitoring costs were applied across all four economic analyses.

The unit cost for each of the services considered for follow-up and monitoring is presented in Table 63. The annual frequency of services received and the proportion of patients assumed to receive each service was based on TA612 (NICE appraisal of neratinib for extended adjuvant treatment of HR+/HER2+ EBC after adjuvant trastuzumab)[148] and is presented in Table 64.

Finally, the model assumed patients who experience a SPM receive the cost of detecting the SPM and exit the model. This cost was derived from a study by Simcock and Heaford (2012) and inflated to 2022/23,[187] in line with NICE TA810.[6]

Table 63: Costs of follow-up and monitoring included in the economic analyses

Service name	Cost	Cost estimation
GP Visit	£49.00	PSSRU 2023; Unit costs for a GP, per surgery consultation lasting 10 minutes
Mammogram	£73.79	NHS Reference Costs 22-23; Outpatient Plain Film, IMAGOP-PF
Oncologist Visit	£144.83	NHS Reference Costs 22-23; Outpatient Consultant Led Non-Admitted Face-to-Face Attendance, Follow-up [WF01A], Clinical Oncology Service
Echocardiography	£95.19	NHS Reference Costs 22-23; Outpatient Electrocardiogram Monitoring or Stress Testing, EY51Z
MUGA scan	£403.26	NHS Reference Costs 22-23; Total Multi-Gated Acquisition [MUGA] Scan, RN22Z.
CT scan	£73.79	NHS Reference Costs 22-23; Outpatient Plain Film, IMAGOP-PF
Mastectomy	£4,069.72	NHS Reference Costs 22-23; Weighted average of unilateral and bilateral major breast procedures, JA20D-F, JA21A-B
Breast Reconstruction	£12,537.71	NHS Reference Costs 22-23; Weighted average of unilateral and bilateral breast reconstruction, JA30Z-31Z, JA34Z-35Z
Multidisciplinary care	£131.27	Simcock and Heaford (2012), inflated to latest cost year using a combination of the Pay and Price Index and NHSCII (Pay & Price) Index
Radiotherapy	£266.96	NHS Reference Costs 22-23; Outpatient Deliver a Fraction of Complex Treatment on a Megavoltage Machine, SC23Z
Complete blood count	£2.75	NHS Reference Costs 22-23; Haematology DAPS05
Electrocardiogram	£95.19	NHS Reference Costs 22-23; Electrocardiogram Monitoring or Stress Testing, EY51Z, Directly accessed diagnostic service
Oncologist consultation	£144.83	NHS Reference Costs 22-23; Outpatient Consultant Led Non-Admitted Face-to-Face Attendance, Follow-up [WF01A], Clinical Oncology Service
Serum chemistry	£1.61	NHS Reference Costs 22-23; Clinical Biochemistry Cost, DAPS04, Directly accessed diagnostic service

Service name	Cost	Cost estimation
X-ray	£112.65	NHS Reference Costs 22-23; Dexa Scan, RD50Z, Diagnostic Imaging
Liver function test	£1.61	NHS Reference Costs 22-23; Clinical biochemistry, DAPS04

Abbreviations: CT: computed tomography; GP: general practitioner; MUGA: multi-gated acquisition; NHS: National Health Service; PSSRU: Personal Social Services Research Unit.

Table 64: Follow-up and monitoring services frequency and percent receiving by state

Service/treatment	Health state	Frequency (per year)	Utilisation rate	Source
Follow-up services				NICE TA612[148]
GP visit	iDFS	Once a year	100%	
	Remission	Once a year from Year 2 onwards	100%	
	DR	Monthly	100%	
Mammogram	iDFS	Once a year during first 4 years	100%	
	NMR	Once a year	100%	
	Remission	Once a year	100%	
Oncologist visit	NMR	Twice a year	100%	
	Remission	Twice a year during first year	100%	
	DR	Once a month	100%	
Echocardiography	NMR	4 times a year	70%	
	Remission	4 times a year during first year	70%	
	DR	Twice a year	70%	
MUGA scan	NMR	4 times a year	30%	
	Remission	4 times a year during first year	30%	
	DR	Twice a year	30%	
CT scan	NMR	Twice a year	75%	
	DR	5 times a year	100%	
Complete blood count	DR	Once a month	100%	NICE TA810[6]
Electrocardiogram	DR	4 times a year	100%	
Oncologist consultation	DR	Once a month	100%	
Serum chemistry	DR	Once a month	100%	
X-ray	DR	Once every 2 months	40%	
Liver function test	NMR	Twice a year	75%	
Subsequent treatments				
Mastectomy	NMR	One-off	100%	
Breast reconstruction	NMR	One-off	100%	
Radiotherapy	NMR	One-off	9.9%	
Multidisciplinary care	SPM	One-off	100%	

Abbreviations: CT: computed tomography; DR: distant recurrence; EBC: early breast cancer; IDFS: invasive disease-free survival; MUGA: multi-gated acquisition; NMR: non-metastatic recurrence; SPM: secondary primary malignancy.

In addition, additional treatment-specific healthcare resources for follow-up and monitoring were included for ribociclib and abemaciclib, as per their SmPCs,[1, 135] as shown in Table 65.

Table 65: Additional treatment-specific healthcare resource use for ribociclib and abemaciclib

Service	Description	Total number of additional services
Ribociclib plus AI		
Complete blood count	Complete blood count should be performed prior to treatment initiation, Q2W for the first 2 cycles, and at the beginning of each of the subsequent 4 cycles.	9
Liver function test	Liver function test should be performed prior to treatment initiation, Q2W for the first 2 cycles, and at the beginning of each of the subsequent 4 cycles.	9
Electrocardiogram	Assess electrocardiogram prior to treatment initiation, during cycle 1, and as clinically indicated.	2
Serum chemistry	Monitoring of serum electrolytes should be performed prior to treatment initiation and at the beginning of the first 6 cycles.	7
Abemaciclib plus ET		
Complete blood count	Complete blood count should be performed prior to treatment initiation, Q2W for the first two months, and Q4W for the next two months, and as clinically indicated.	7
Liver function test	Liver function test should be performed prior to treatment initiation, Q2W for the first two months, and Q4W for the next two months, and as clinically indicated.	7

Abbreviations: ET: endocrine therapy; QXW: every X weeks.
Source: Ribociclib [draft] SmPC;[1] Abemaciclib SmPC.[135]

B.3.5.5 Adverse reaction unit costs and resource use

The costs associated with the treatment of AEs were calculated by multiplying the incidence of AEs by the expected cost of these events. Further details of the AEs included in the model are presented in Section B.3.3.5. The unit costs of treating each AE were assumed to cost the equivalent of one Medical Oncology Consultant face-to-face appointment (NHS reference costs ([2022-23]), as presented in Table 66.

Table 66: AE costs included in the economic analyses

AE	Unit cost	Source
Alanine aminotransferase increased	£190.53	NHS Reference Costs 22-23; WF01A, Consultant Led, Medical Oncology Non-admitted Face to Face Attendance, Follow Up
Diarrhoea	£190.53	
Leukopenia	£190.53	
Lymphopenia	£190.53	
Neutropenia	£190.53	

Abbreviations: AE: adverse event; NHS: national health service.

B.3.5.6 Miscellaneous unit costs and resource use

End-of-life costs were included in the economic analysis for all patients modelled to enter the

death state, excluding those who entered the SPM absorbing state as death was not modelled for that population. The same end-of-life cost was applied across all four economic analyses.

The end-of-life cost was calculated as a weighted average of hospital, hospice and at home with community support costs based on the proportions and costs provided in the NICE CG81 guideline (Table 67).

Table 67: End-of-life cost calculations in the model

Terminal care	% of patients in each care setting	Cost	Source
Hospital	40.00%	£6,732.04	NICE CG81 clinical guidelines;[188] costs are inflated to latest cost year using a combination of the Pay and Price Index and NHSCII (Pay & Price) Index.
Hospice	10.00%	£8,392.88	
At home with community support	50.00%	£3,473.31	
Total cost	**£5,268.76**		

Abbreviations: NHSCII: NHS Cost Inflation Index; NICE: National Institute for Health and Care Excellence.

B.3.6 Severity

The use of ribociclib plus AI in HR+/HER2– EBC at high risk of recurrence does not meet the NICE severity modifier criteria and therefore this section is not applicable.

B.3.7 Uncertainty

The following represent areas of uncertainty within the economic analysis:

Length of follow-up data from NATALEE: As the median duration of follow-up at the latest data cut of NATALEE (April 2024) was [redacted] months and, given the lack of alternative evidence for long-term iDFS for ribociclib plus AI and the relevant comparators to this submission in a population consistent with NATALEE, there is uncertainty regarding the longer-term survival outcomes. Parametric distribution extrapolations for iDFS were therefore used, which, despite curve selection being based on statistical goodness-of-fit, visual fit, and primarily clinical plausibility, remain associated with inherent uncertainty. To explore this uncertainty, scenario analyses were conducted using several alternative iDFS distributions for both ribociclib plus AI and ET, as well as abemaciclib plus ET (in Population 4).

Use of NATALEE AI arm to inform efficacy of ET: Across all four economic analyses, iDFS efficacy for the comparator ET was informed by AI arm of the NATALEE trial. This represents a limitation given the AI arm of the NATALEE trial comprised anastrozole and letrozole, whereas in UK clinical practice, two further ETs (exemestane and tamoxifen) may also be prescribed. As evidence suggests tamoxifen is less effective than AIs in reducing disease recurrence in EBC (see Appendix M.1), a weighted HR was applied to the AI iDFS curve from NATALEE to reflect any differential efficacy for the proportion of patents receiving these therapies. While the HR for tamoxifen vs AIs used to inform this adjustment was identified via a TLR (see Appendix M.1), uncertainty arising from this assumption remains. As such, two further scenario analyses were conducted whereby the HR for tamoxifen vs AIs was set to two alternative values.

Uncertainty in the modelling of the DR health state: As described in Section B.3.2.2, the DR health state was modelled using two PSM frameworks (for the ET-sensitive and ET-resistant DR

substates, respectively), with the output of the PSMs (in terms of LYs, QALYs and costs) applied to patients entering the DR health state within the semi-Markov cohort state-transition model. This approach is inherently associated with some uncertainty as it relies on a number of assumptions, principally the efficacy of subsequent therapies (other than ribociclib) received within the DR health state. Nevertheless, as detailed in in Section B.3.2.2, this approach was taken for a number of reasons and was deemed more granular and therefore more transparent than other methods, for example using a lump-sum approach. Scenario analyses were conducted to explore the impact of alternative PFS and OS curve choices for ribociclib in the DR health state (which in turn adjusts the efficacy of other subsequent therapies), as well as alternative HRs for other subsequent therapies that were derived from literature sources.

Comparison vs abemaciclib plus ET in Population 4: Finally, in the absence of head-to-head data between ribociclib plus AI and abemaciclib plus ET and ET in Population 4 (node-positive high-risk eligible for abemaciclib), iDFS for patients receiving ribociclib plus AI and ET in Population 4 (node-positive high-risk eligible for abemaciclib) was based the MAIC conducted between NATALEE and Cohort 1 of the monarchE trial (see Section B.2.8) which, despite adjusting for all available baseline characteristics, may still be limited by unreported or unobserved confounding factors. This is an inherent limitation of the MAIC approach.

B.3.8 Managed access proposal

Not applicable.

B.3.9 Summary of base case analysis inputs and assumptions

B.3.9.1 Summary of base case analysis inputs

A summary of the base case model inputs is provided in Table 68 for Population 1 (NATALEE ITT). Appendix U presents the variables that vary from the base case for the three economic subgroup analyses (Population 2 [NATALEE node-positive], Population 3 [NATALEE node-negative] and Population 4 [node-positive high-risk eligible for abemaciclib], respectively). Variables not presented in Appendix U do not differ from the base case (Population 1 [NATALEE ITT]) model inputs.

Table 68: Summary of base case model inputs for Population 1 (NATALEE ITT)

Variable	Value/source		Section in submission
Model settings			
Discount rate, %	3.5		Section B.3.2.1
Time horizon	50 years		
Perspective	UK NHS and PSS		
Treatment dosages			
Intervention and comparator: treatment mix	***Ribociclib plus AI***	***ET***	
Ribociclib	[redacted]	N/A	Section B.3.5.1
Letrozole	[redacted]	[redacted]	
Anastrozole	[redacted]	[redacted]	
Exemestane	[redacted]	[redacted]	

Tamoxifen	N/A	[redacted]	
Goserelin	[redacted]	[redacted]	
Zoledronic acid	[redacted]	[redacted]	
Intervention and comparator: RDI	***Ribociclib plus AI***	***ET***	
Ribociclib	[redacted]	N/A	Section B.3.5.1
Letrozole	[redacted]	[redacted]	
Anastrozole	[redacted]	[redacted]	
Exemestane	[redacted]	[redacted]	
Tamoxifen	N/A	[redacted]	
Goserelin	[redacted]	[redacted]	
Zoledronic acid	[redacted]	[redacted]	
Subsequent therapies: RDI			
Ribociclib plus fulvestrant			Section B.3.5.2
Ribociclib (metastatic)	[redacted]		
Fulvestrant	[redacted]		
Palbociclib plus fulvestrant			
Palbociclib	[redacted]		
Fulvestrant	[redacted]		
Abemaciclib plus fulvestrant			
Abemaciclib	[redacted]		
Fulvestrant	[redacted]		
Everolimus plus exemestane			
Everolimus	[redacted]		
Exemestane	[redacted]		
Palbociclib plus AI			
Palbociclib	[redacted]		
Letrozole	[redacted]		
Ribociclib plus AI			
Ribociclib (metastatic)	[redacted]		
Letrozole	[redacted]		
Abemaciclib plus AI			
Abemaciclib	[redacted]		
Anastrozole	[redacted]		
Letrozole	[redacted]		
Exemestane	[redacted]		
Tamoxifen	[redacted]		
Capecitabine	[redacted]		
Alpelisib			
Alpelisib	[redacted]		
Fulvestrant	[redacted]		
Paclitaxel	[redacted]		
Goserelin	[redacted]		

Post-progression treatment mix by health state	***Ribociclib plus AI***	***ET***	
NMR			Section B.3.5.2
Letrozole	[redacted]	[redacted]	
Anastrozole	[redacted]	[redacted]	
Exemestane	[redacted]	[redacted]	
Tamoxifen	[redacted]	[redacted]	
Goserelin	[redacted]	[redacted]	
DR ET-sensitive			
Ribociclib plus AI	[redacted]	[redacted]	
Palbociclib plus AI	[redacted]	[redacted]	
Abemaciclib plus AI	[redacted]	[redacted]	
Capecitabine	[redacted]	[redacted]	
DR ET-resistant			
Ribociclib plus fulvestrant	[redacted]	[redacted]	
Palbociclib plus fulvestrant	[redacted]	[redacted]	
Abemaciclib plus fulvestrant	[redacted]	[redacted]	
Everolimus plus exemestane	[redacted]	[redacted]	
Capecitabine	[redacted]	[redacted]	
Paclitaxel	[redacted]	[redacted]	
Alpelisib	[redacted]	[redacted]	
Clinical parameters			
Clinical effectiveness	***Ribociclib plus AI***	***ET***	
iDFS	Exponential	Exponential	Section B.3.3.3
TTD	Ribociclib: NATALEE Kaplan-Meier AI: Weibull (R)	Weibull (R)	
Remission	A monthly transition probability of 0.00760 from remission to DR was derived from TA632[136], based on clinical expert feedback		
DR health states (ET-sensitive and ET-sensitive)	Clinical effectiveness estimates for the DR health states were based on the MONALEESA-2 (ET-sensitive) MONALEESA-3 (ET-resistant) trials. HRs for different DR treatments were primarily derived from Shao *et al*. (2024)[142]		
Adverse events	***Ribociclib plus AI***	***ET***	
Alanine aminotransferase increased	[redacted]	[redacted]	Section B.3.4.1
Diarrhoea	0.63%	0.12%	
Leukopenia	[redacted]	[redacted]	
Lymphopenia	[redacted]	[redacted]	
Neutropenia	[redacted]	[redacted]	
Utility inputs			

Health state utility values		
On-treatment iDFS	0.7620	Section B.3.4.5
Off-treatment iDFS	0.7367	
NMR	0.6818	
ET-sensitive DR PFS	0.6190	
ET-sensitive DR PPS	0.5944	
ET-resistant DR PFS	0.6190	
ET-resistant DR PPS	0.5755	
Adverse events		
Alanine aminotransferase increased	-0.005	Section B.3.4.4
Diarrhoea	-0.103	
Leukopenia	-0.003	
Lymphopenia	-0.007	
Neutropenia	-0.007	
Cost inputs		
Adjuvant and subsequent therapies (cost per unit, package, or vial)		
Ribociclib	PAS price: £[redacted]	Section B.3.5.2
Letrozole	£0.86	
Anastrozole	£0.50	
Goserelin	£70.00	
Abemaciclib	£2,950.00	
Exemestane	£4.20	
Zoledronic acid	£4.00	
Tamoxifen	£2.87	
Fulvestrant	£55.32	
Palbociclib	£2,950.00	
Everolimus	£488.32	
Capecitabine	£22.51	
Alpelisib	PAS price: £[redacted]	
Paclitaxel	£9.13	
Post-progression drug costs in the DR health states		
Monthly cost	£1,170.00	Section B.3.5.2
Drug administration		
SC administration	£47.00	Section B.3.5.3
IV administration (first attendance)	£217.22	
IV administration (subsequent attendance)	£249.23	
Oral administration	£0.00	
IM administration: loading dose total cost	£315.03	
IM administration: subsequent doses total cost	£79.58	
Follow-up and monitoring		

GP visit	£49.00	Section B.3.5.4
Mammogram	£73.79	
Oncologist visit	£144.83	
Echocardiography	£95.19	
MUGA scan	£403.26	
CT scan	£73.79	
Mastectomy	£4,069.72	
Breast reconstruction	£12,537.71	
Multidisciplinary care	£131.27	
Radiotherapy	£266.96	
Complete blood count	£2.75	
Electrocardiogram	£95.19	
Oncologist consultation	£144.83	
Serum chemistry	£1.61	
X-ray	£112.65	
Liver function test	£1.61	

Abbreviations: AI: aromatase inhibitor; CT: computational tomography; DR: distant recurrence; ET: endocrine therapy; GP: general practitioner; iDFS: invasive disease-free survival; IM: intramuscular; IV: intravenous; MUGA: multi-gated acquisition; NMR: non metastatic recurrence; PFS: progression free survival; PPS: post progression survival; R: restricted; RDI: relative dose intensity; SC: subcutaneous; TTD: time to treatment discontinuation.

B.3.9.2 Assumptions

An overview of the assumptions adopted within the economic analyses is provided in Table 69.

Table 69: Summary of economic analysis assumptions

Model element	Assumption and justification	Scenario analyses	Section in submission
Efficacy of ribociclib plus AI (iDFS health state)	iDFS efficacy of ribociclib plus AI in all four economic analyses was informed by iDFS data for the ribociclib plus AI arm of the NATALEE trial, with data derived separately for each of the respective populations, and extrapolated to estimate long-term iDFS beyond the follow-up of the trial.	Scenario analyses were conducted for all four populations to assess the impact of alternative parametric distributions fit to the ribociclib plus AI iDFS data.	Section B.3.3.3
Efficacy of ET (iDFS health state)	iDFS efficacy of the comparator ET in all four economic analyses was informed by the AI arm of the NATALEE trial, with data derived separately for each of the respective populations, and extrapolated to estimate long-term iDFS beyond the follow-up of the trial. The only therapies received in the AI arm of the NATALEE trial were anastrozole or letrozole. To capture the efficacy of exemestane and tamoxifen, a weighted HR was applied to the AI iDFS curve from NATALEE to reflect any differential efficacy for the proportion of patents receiving these therapies. • For exemestane, it was assumed that all AIs would have similar efficacy, and therefore the HR applied for patients receiving exemestane was 1. For tamoxifen, evidence from a TLR on the efficacy of tamoxifen vs AIs (see Appendix M.1) suggests that AI therapies are more effective than tamoxifen, particularly in reducing disease recurrence in HR+/HER2– EBC. As such, a HR of 1.10 was applied for tamoxifen, based on the study by Liao *et al.* (2022),[101] identified in the TLR. The reduced efficacy of tamoxifen vs AIs was also validated by UK clinical experts at a recent advisory board held in September 2024 (see Appendix Q.3)	Scenario analyses were conducted for all four populations to assess the impact of alternative parametric distributions fit to the AI iDFS data. Further scenario analyses were conducted for all four populations whereby the HR applied to the AI iDFS curve for the proportion of patients receiving tamoxifen was: • 1.45, based on a recent study by Janni *et al*. (2023).[140] Whilst this study was not identified in the TLR (because it is a conference presentation), it represents a recent, comprehensive meta-analysis comparing the efficacy of tamoxifen to AIs in HR+/HER2– EBC • 1, based on a conservative assumption that the efficacy of tamoxifen and AIs would be the same	Section B.3.3.3
Efficacy of abemaciclib plus ET and ET (iDFS health state)	iDFS for abemaciclib plus ET was assumed equivalent to ribociclib plus AI, by applying a HR of 1 to the matched and weighted ribociclib plus AI Kaplan-Meier curve from the NATALEE-selected population of the NATALEE trial. For ET, the matched and weighted iDFS curve for AI derived from the MAIC was utilised, with the same adjustment for tamoxifen applied as detailed above.	N/A.	Appendix R.1.4

in Population 4			
Treatment effect waning	Across all four economic analyses, a treatment waning effect was assumed for ribociclib plus AI, and for abemaciclib plus ET in Population 4. Based on the results of the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial,[134] it was assumed that there would be a "carryover benefit" of a constant treatment effect lasting up to 8 years, after which the treatment effect was modelled to wane. The hazard rate of recurrence for ribociclib after 8 years was calculated as a weighted average of the hazard rate from the parameterised ribociclib plus AI iDFS curve and that of the ET iDFS curve, adjusted over the specified waning period such that the weight applied to the hazard rates of the ET alone arm was equal to one at the end of the waning period (the point at which the iDFS event rate was equal to general population mortality). This approach is consistent with the approach used to inform decision making in TA810,[6] and was validated by UK clinical experts at a recent advisory board held in September 2024, where the clinical experts noted that they would expect the carryover benefit to last between 5–10 years (see Appendix Q.3). Scenario analyses were therefore conducted to test the impact of a constant treatment effect lasting for 5 or 10 years, in line with this clinical expert feedback.	Scenario analyses were conducted for all four populations for ribociclib plus AI, and for abemaciclib plus ET in Population 4, whereby: • The treatment effect was assumed to be constant, and life-long, with no treatment waning • The treatment effect was assumed to be constant up to 10 years • The treatment effect was assumed to be constant up to 5 years • The treatment effect was assumed to be constant up to 5 years, with treatment waning from Years 5–8 only	Section B.3.3.4
Transitions from NMR health state	Across all four economic analyses, it was assumed that: • Transitions from NMR to DR would not be possible, and therefore the probability of transitioning between these health states was zero. This was based on the modelling approach used to inform decision making in TA810.[6] • After 12 months, all patients in the NMR health state transition to the remission health state or die, in line with the approach adopted in TA632[136] and TA810,[6] and validated by UK clinical experts at a recent advisory board held in September 2024 (see Appendix Q.3). • Transitions from NMR to death were assumed to be the maximum of either the iDFS probability of death or general population mortality	N/A.	Section B.3.2.2
Transitions from	Across all four economic analyses, the probability of transitioning from the remission health state to DR was based on the previously adopted transition	N/A.	Section B.3.2.2

remission health state	probability estimate in NICE TA632[136] and TA810,[6] derived from Hamilton *et al.* (2015),[137] and assumed to remain constant over time.		
Efficacy of post-progression therapies in DR health state	Across all four economic analyses, LYs, time on treatment, QALYs, and costs within the DR health state were calculated within a PSM framework based on PFS, TTD, and OS data from clinical trials for ribociclib in the advanced or metastatic breast cancer setting (MONALEESA-2 for the ET-sensitive substate and MONALEESA-3 for the ET-resistant substate).[87, 133] For patients receiving other treatments, survival curves were estimated by applying estimated HRs for PFS, OS and TTD for the given comparator vs ribociclib plus AI/fulvestrant to the corresponding survival curve for ribociclib plus AI/fulvestrant, based on a published NMA by Shao *et al.* (2024).[142] Where treatments were not included in the NMA by Shao *et al.* (2024),[142] the following assumption was made in the ET-sensitive substate: • For capecitabine, OS, PFS and TTD HRs were derived from the RIGHT CHOICE trial.[143] As this trial is in patients with aggressive breast cancer, a scenario analysis was conducted to explore the impact of any uncertainty surrounding these HRs.	Scenario analyses were conducted across all four populations to assess the impact of alternative parametric distributions fit to the ribociclib plus fulvestrant (MONALEESA-2) and ribociclib plus AI (MONALEESA-3) PFS and OS KM data. In addition, scenario analyses were conducted across all four populations whereby PFS/OS/TTD HRs for capecitabine were assumed equivalent to letrozole/anastrozole.	Section B.3.2.2 and Section B.3.3.3
Treatment mix of AI/ET (iDFS health state)	The iDFS treatment mix of AI (as part of ribociclib plus AI) and the ET comparator in Population 1, and for AI (as part of ribociclib plus AI), ET (as part of abemaciclib plus ET) and the ET comparator in Population 4, were based on clinical expert feedback from a recent advisory board held in September 2024 (see Appendix Q.3), to ensure generalisability to UK clinical practice. The proportion of patients receiving goserelin as part of the relevant AI iDFS treatment mixes in combination with ribociclib was based on clinical expert feedback UK from a recent advisory board held in September 2024 and adjusted based on the values from the literature (see Appendix Q.3). The proportion of patients receiving goserelin in addition to abemaciclib plus ET in Population 4 was assumed to be equal to the proportion of patients receiving goserelin in addition to ribociclib plus AI in Population 4. The proportion of patients receiving zoledronic acid as part of the relevant AI/ET iDFS treatment mixes was based on the proportion of patients receiving zoledronic acid in the NATALEE trial (ITT population) and assumed to apply across all four populations.	Scenario analyses were conducted in Populations 1, 2, and 3 whereby: • the iDFS treatment mix of AI (as part of ribociclib plus AI) and the ET comparator were based on those estimated by clinical experts for Population 4. A scenario analysis was conducted in Population 4, whereby: • the iDFS treatment mix of AI (as part of ribociclib plus AI), ET (as part of abemaciclib plus ET) and the ET comparator were based on those estimated by clinical experts for Population 1. Here, ET (as part of abemaciclib plus ET) was	Section B.3.5.1

	The iDFS treatment mix of AI (as part of ribociclib plus AI) and the ET comparator for Populations 2 and 3 were assumed to be the same as those for Population 1.	based on the treatment mix of AI as part of ribociclib plus AI) in Population 1. The proportion of patients receiving tamoxifen was set to 0%, as per Population 1. In addition, a scenario analysis was conducted across all four populations to assess the impact of the proportion of patents receiving goserelin, whereby: • the proportion of patients receiving goserelin as part of ribociclib plus AI in all four populations was assumed to be based on the NATALEE trial (ITT population; April 2024 data cut): [redacted] in the ribociclib plus AI arm (also applied for abemaciclib plus ET in Population 2) and [redacted] for the ET arm	
Treatment mix of AI/ET (NMR health state)	The same treatment mix of ET in the NMR health state was assumed across all four populations, with the treatment mix aligned to the treatment mix utilised within the iDFS health state for Population 1 (NATALEE ITT). This is with the exception of zoledronic acid, which was not assumed to be received in the NMR health state, given its maximum treatment duration of 3 years, and in line with the approach taken in TA810.[6]	N/A.	Section B.3.5.2
Treatment mix (DR health state)	ET-resistant and ET-sensitive DR treatment mixes in Population 1 were based on UK clinical expert feedback received at the Company advisory board held in September 2024 (see Appendix Q.3, respectively). It was assumed that 45% of patients in the ribociclib plus AI arm of the model would receive retreatment with a CDK4/6 inhibitor in the ET-sensitive DR health state. This represents half of the proportion assumed to receive a CDK4/6 inhibitor in the ET-sensitive DR health state in the ET arm of the	Scenario analyses were conducted for all four populations whereby: • 90% of the ribociclib plus AI arms (and abemaciclib plus ET arm in Population 4) received CDK4/6 rechallenge (in line with the ET arm) • 70% of the ribociclib plus AI arms (and abemaciclib plus ET arm in	Section B.3.5.2

	model (90%). Given this may change in the near future in UK clinical practice, scenario analyses were conducted to explore the impact of this. The treatment mixes for ribociclib plus AI and ET in Populations 2, 3 and 4 were assumed to be the same as those estimated for Population 1. The treatment mix for abemaciclib plus ET in Population 4 was assumed to be the same as that estimated for ribociclib plus AI in Population 1.	Population 4) received CDK4/6 rechallenge	
RDI	Across all four economic analyses, the RDI for ribociclib was assumed to be [redacted] derived from the NATALEE trial (ITT population; April 2024 data cut). The RDI for ribociclib was not assumed to differ between populations. In Population 1, the RDIs for AI (as part of ribociclib plus AI) and ET treatments (including goserelin) were derived from the NATALEE trial (ITT population; April 2024 data cut). In the absence of RDI data for exemestane, this was assumed to be the same as for anastrozole and letrozole ([redacted]). In the absence of RDI for tamoxifen and zoledronic acid, this was assumed to be [redacted] For Populations 2–4, the same RDIs for AI (as part of ribociclib plus AI) and ET were assumed as per Population 1. In Population 4, in the absence of RDI data for abemaciclib, this was calculated from RDI data for ribociclib (treatment pauses only) from the NATALEE trial (ITT population; April 2024 data cut). The RDIs for ET (as part of abemaciclib plus ET) were assumed to be 100%, based on what was assumed in TA810.[6] The RDIs for ribociclib plus AI and ET alone in Population 4 were assumed to be the same as those in Population 1.	Scenario analyses were conducted for all four populations whereby: • The RDI for all AI/ET therapies was set to 100% A scenario analysis was conducted in Population 4 whereby: • The RDI for abemaciclib was assumed to equal the RDI for ribociclib, and the RDIs for ET (as part of abemaciclib plus ET) were assumed to equal the RDIs for the relevant AIs in the ribociclib plus AI arm (with tamoxifen and zoledronic acid assumed to be [redacted]	Section B.3.5.1
Adjustment of drug wastage with down-dosing	In Population 4, for patients experiencing toxicities with abemaciclib, down-dosing is adopted in clinical practice, whereby patients receive abemaciclib at a lower dose. To account for this within the model, it was assumed that the cost associated with abemaciclib pack wastage would be accrued by 50% of patients who required down-dosing given that, on average, the down-dosing would occur halfway through the package at the original dose being consumed. The proportion of patients requiring down-dosing with abemaciclib (single down-dose: 29.81%; two down-doses: 13.94%) was based on analyses of the monarchE trial reported by Goetz *et al.* (2024).[173] Given the pack format, dosing and linear pricing of ribociclib, this wastage assumption was not relevant for ribociclib.	N/A.	Section B.3.5.1

Time on treatment (ribociclib [as part of ribociclib plus AI])	Across all four economic analyses, time on treatment with ribociclib was estimated using the Kaplan-Meier curve for TTD for the ribociclib part of the ribociclib plus AI arm directly from the NATALEE trial (April 2024 data cut), with data derived separately for all four populations. Given the maturity of the TTD data for ribociclib, no scenario analyses were conducted for ribociclib time on treatment.	N/A	Section B.3.3.3
Time on treatment (AI [as part of ribociclib plus AI])	Across all four economic analyses, time on treatment with AI (as part of ribociclib plus AI) was estimated by fitting parametric survival distributions to the Kaplan-Meier curve for TTD for the AI part of the ribociclib plus AI arm in the NATALEE trial (April 2024 data cut), with data derived separately for all four populations.	Scenario analyses were conducted for all four populations to assess the impact of alternative parametric distributions fit to the Kaplan-Meier curve for TTD for the AI part of the ribociclib plus AI arm in the NATALEE trial.	Section B.3.3.3
Time on treatment (ET)	Across all four economic analyses, time on treatment with ET was estimated by fitting parametric survival distributions to the Kaplan-Meier curve for TTD for the ET arm in the NATALEE trial (April 2024 data cut), with data derived separately for all four populations. In Population 4, given the lack of data on time on treatment with ET (as part of abemaciclib plus ET), this was assumed to be equal to that for AI when received in combination with ribociclib.	Scenario analyses were conducted for all four populations to assess the impact of alternative parametric distributions fit to the Kaplan-Meier curve for TTD for the ET arm in the NATALEE trial.	Section B.3.3.3
Time on treatment (abemaciclib)	In Population 4, time on treatment with abemaciclib (as part of abemaciclib plus ET) was estimated using the Kaplan-Meier curve for TTD for abemaciclib from the monarchE trial.[141]	A scenario analysis was conducted in Population 4, whereby TTD for abemaciclib was assumed equal to TTD for ribociclib (but with the 2-year maximum treatment duration for abemaciclib applied).	Appendix R.2.4
Maximum duration of treatment (AI/ET)	Across all four economic analyses, the maximum time on treatment for AI (as part of ribociclib plus AI), ET and ET (as part of abemaciclib plus ET in Population 4 only) and was assumed to be 5 years, based on the maximum duration of treatment permitted for AI/ET in the NATALEE trial.	Clinical experts indicated that patients with HR+/HER2– EBC at high risk of recurrence might receive AI/ET for up to 10 years (see Appendix Q.2). Scenario analyses were therefore conducted for all four populations whereby: • Maximum time on treatment for AI/ET: 7 years	Section B.3.5.1

		• Maximum time on treatment for AI/ET: 10 years	
Maximum duration of treatment (ribociclib plus AI)	Across all four economic analyses, the maximum time on treatment for ribociclib was assumed to be 3 years, based on the maximum duration of treatment permitted for ribociclib in the NATALEE trial.	N/A	Section B.3.5.1
Maximum duration of treatment (abemaciclib plus ET)	In Population 4 (node-positive high-risk eligible for abemaciclib), the maximum duration of treatment for abemaciclib was assumed to be 2 years, based on the SmPC for abemaciclib and the maximum duration of treatment permitted for abemaciclib in the monarchE trial (Cohort 1).	N/A	Section B.3.5.1
Treatment costs for PPS treatments in DR health state	Across all four economic analyses, a monthly estimate of treatment costs for PPS treatments was applied across both the ET-resistant and ET-sensitive DR health state. This was assumed to be £1,170, based on the mid-point of the Appraisal Committee's preferred assumptions in TA496 (the Appraisal Committee concluded that it would consider costs in the region of £1,140 to £1,200 in its decision making).[5]	N/A	Section B.3.5.2
Drug acquisition and administration costs	All drug acquisition costs were derived from the BNF. In all four economic analyses, all comparators were incorporated at list price, and ribociclib and alpelisib (as Novartis drugs) were incorporated at PAS price.	N/A	Section B.3.5.1
Resource use estimates	Resource use estimates were estimated by health state, and were assumed to be the same across all four economic analyses. The annual frequency of services received and the proportion of patients assumed to receive each service was based on TA612 (NICE appraisal of neratinib for extended adjuvant treatment of HR+/HER2+ EBC after adjuvant trastuzumab).[148] Additional resource use estimates were applied for ribociclib plus AI (across all four populations) and abemaciclib plus ET (in Population 4) based on their respective SmPCs.[135] Whilst the SmPC for ribociclib recommends 3 ECGs, Novartis understand that this will be reduced to 2 once ribociclib receives its marketing authorisation extension in this indication.	N/A	Section B.3.5.4

	The costs associated with each resource use were derived from the most recent sources, including NHS reference costs (2022-23) and the PSSRU.		
AE frequency	AEs considered in the model included all-cause grade 3+ AEs with an incidence ≥5% for any of the comparators of interest. Grade 1–2 events were not considered because they are generally self-limiting and are therefore not likely to be associated with substantial treatment costs or reductions in HRQoL. Across all four economic analyses, the frequency of all-cause grade 3+ AEs with an incidence ≥5% for ribociclib plus AI and ET was derived from the NATALEE trial (April 2024 data cut), with data derived separately for each of the respective populations. It was assumed that the AEs experienced within the AI arm of NATALEE would be representative of the AEs expected to be experienced with ET in clinical practice. In Population 4, the frequency of all-cause grade 3+ AEs with an incidence ≥5% for abemaciclib plus ET were derived from the monarchE trial.[108]	N/A	Section B.3.3.5
AE costs	Across all four economic analyses, the treatment of all all-cause grade 3+ AEs with an incidence ≥5% was assumed to cost the equivalent of one Medical Oncology Consultant face-to-face appointment (NHS reference costs ([2022-23]).	N/A	Section B.3.5.5
Health state utility values	The same health state utility values were used across all four economic analyses, derived from the NATALEE (ITT population). The iDFS (on-treatment: 0.7620; off-treatment: 0.7367) and NMR (0.6818) health state utility values were derived from EQ-5D-5L data collected directly in NATALEE (ITT population) and mapped onto the EQ-5D-3L UK value set using the mapping function developed by Hernández Alava *et al.* (2017) through the NICE Decision Support Unit (DSU), using the EEPRU dataset (Hernández Alava *et al.* [2020]).[153-155] The remission health state utility value was assumed to equal the health state utility value for iDFS off-treatment, based on assumption made in TA810.[6] The ET-resistant and ET-sensitive DR PFS health state utility values were assumed equal to the overall DR health state utility value derived from EQ-5D-5L data collected directly in NATALEE (ITT population) and mapped onto the EQ-5D-3L UK value set as above.	A scenario analysis was conducted in all four populations whereby: • iDFS and NMR health state utility values were based on those used in TA810[6] (iDFS: 0.782; NMR: 0.76)	Section B.3.4.5

	The ET-resistant and ET-sensitive DR PPS health state utility values were calculated by taking the ratio of the utility values estimated for the PFS and PPS health states of the previous ribociclib evaluations based on MONALEESA-2 and MONALEESA-3,[87, 133] and applying that ratio of the utility value for the overall DR health state utility value derived from EQ-5D-5L data collected directly in NATALEE (ITT population) and mapped onto the EQ-5D-3L UK value set as above.		
AE disutilities and duration	For patients receiving ET, the mean utility values for on-treatment iDFS generated from the AI arm of NATALEE were assumed to capture the effects of AEs on HRQoL. As such, no other adjustments for AE disutilities were included for ET to avoid double-counting. For patients receiving either ribociclib plus AI or abemaciclib plus ET (Population 4 only), a QALY decrement was applied based on estimates of the disutilities associated with AEs, differences in incidence of AEs between ET and ribociclib plus AI, and the expected duration of AEs. The disutilities for each AE were based on those used to inform decision making in TA810,[6] which were derived from NICE evaluations and values from the literature. The duration of all AEs (and therefore the duration of the disutility application) was based on those used to inform decision making in TA810,[6] which were derived from previous NICE evaluations and values from the literature.	N/A	Section B.3.4.4

Abbreviations: AE; adverse events; EQ-5D: EuroQoL-5dimensions; ET: endocrine therapy; ITT: intention-to-treat; NICE: National Institute for Health and Care Excellence; OS: overall survival; PFS: progression-free survival; TTD: time-to-treatment discontinuation.

B.3.10 Base case results: Population 1 (NATALEE ITT)

Deterministic base case results for the economic analysis of ribociclib plus AI vs ET in Population 1 (NATALEE ITT) are presented in Table 70 (ICER) and Table 71 (net health benefit).

In the deterministic base case analysis in Population 1 (NATALEE ITT), ribociclib plus AI (with the PAS for ribociclib) was associated with [redacted] more QALYs and reduced total costs of [redacted] in comparison to ET, resulting in ribociclib plus AI dominating ET in this population (Table 70). NHB results at both a £20,000 and £30,000 willingness-to-pay (WTP) threshold are positive, indicating ribociclib plus AI represents a cost-effective use of NHS resources vs ET in Population 1 (NATALEE ITT).

Table 70: Deterministic base case results: ribociclib plus AI vs ET – Population 1 (NATALEE ITT)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ET	[redacted]	14.94	[redacted]				
Ribociclib plus AI	[redacted]	15.59	[redacted]	[redacted]	0.65	[redacted]	Dominant

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; Incr: incremental; ITT: intention to treat; LYG: life years gained; QALYs: quality-adjusted life years.

Table 71: Deterministic NHB results: ribociclib plus AI vs ET – Population 1 (NATALEE ITT)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	NHB at £20,000	NHB at £30,000
ET	[redacted]	[redacted]				
Ribociclib plus AI	[redacted]	[redacted]	[redacted]	[redacted]	0.64	0.60

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; Incr: incremental; ITT: intention to treat; LYG: life years gained; QALYs: quality-adjusted life years; NHB: net health benefit.

B.3.11 Exploring uncertainty

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted in order assess the simultaneous effect of uncertainty in the different model parameters and to demonstrate whether the model results were robust to those variations. A Monte-Carlo simulation with 1,000 iterations was performed where model inputs were randomly sampled from the specified probability distributions. Estimates of model parameters based on the uncertainty in the source data (where data availability permitted). Where no such data were available, SEs were estimated as 10% of the mean value.

An ICER convergence plot for the PSA in Population 1 (NATALEE ITT) is presented in Figure 38 below which demonstrates that the cumulative ICER stabilised after approximately 500 iterations.

Figure 38: ICER convergence plot for the PSA in Population 1 (NATALEE ITT)

Abbreviations: ICER: incremental cost-effectiveness ratio; ITT: intention to treat; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Probabilistic base case results for the economic analysis of ribociclib plus AI vs ET in Population 1 (NATALEE ITT) are presented in Table 72 (ICER) and Table 73 (net health benefit).

In the probabilistic base case analysis in Population 1 (NATALEE ITT), ribociclib plus AI (with the PAS for ribociclib) was associated with [redacted] more quality-adjusted life years (QALYs) and decreased total costs of [redacted] in comparison to ET, resulting in ribociclib plus AI dominating ET in this population (Table 72). NHB results at both a £20,000 and £30,000 willingness-to-pay (WTP) threshold are positive, indicating ribociclib plus AI represents a cost-effective use of NHS resources vs ET in Population 1 (NATALEE ITT).

Table 72: Probabilistic base case results: ribociclib plus AI vs ET – Population 1 (NATALEE ITT)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ET	[redacted]	15.03	[redacted]				
Ribociclib plus AI	[redacted]	15.67	[redacted]	[redacted]	0.64	[redacted]	Dominant

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; Incr: incremental; ITT: intention to treat; LYG: life years gained; QALYs: quality-adjusted life years.

Table 73: Probabilistic NHB results: ribociclib plus AI vs ET – Population 1 (NATALEE ITT)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	NHB at £20,000	NHB at £30,000
ET	[redacted]	[redacted]				
Ribociclib plus AI	[redacted]	[redacted]	[redacted]	[redacted]	0.63	0.59

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; Incr: incremental; ITT: intention to treat; QALYs: quality-adjusted life years; NHB: net health benefit.

A scatter plot showing the incremental costs and QALYs from the 1,000 iterations of the PSA for ribociclib plus AI vs ET in Population 1 (NATALEE ITT) is presented in Figure 39 and indicate a [redacted] and [redacted] likelihood of ribociclib plus AI being cost-effective vs ET at WTP thresholds of £20,000 and £30,000 per QALY gained, respectively.

Figure 39: PSA scatter plot for ribociclib plus AI vs ET – Population 1 (NATALEE ITT)

[redacted]

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; ITT: intention to treat; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years; WTP: willingness to pay.

The cost-effectiveness acceptability curve (CEAC) for ribociclib plus AI vs ET in Population 1 (NATALEE ITT) is presented in Figure 40.

Figure 40: CEAC for ribociclib plus AI vs ET – Population 1 (NATALEE ITT)

[redacted]

Abbreviations: AI: aromatase inhibitor; CEAC: cost-effectiveness acceptability curve; ET: endocrine therapy;

ITT: intention-to-treat; QALY: quality-adjusted life year; ribo: ribociclib; WTP: willingness to pay.

Deterministic sensitivity analysis

DSA was undertaken to explore the impact of changing key model parameter values on the NHB. Parameters were varied by +/- 10% in order to assess the relative impact of these parameters on the cost-effectiveness estimates.

The tornado diagram showing the key drivers of the DSA in the base case economic analysis of ribociclib plus AI vs ET in Population 1 (NATALEE ITT) is presented in Figure 41. The largest model drivers were PFS HRs applied for capecitabine in the ET-sensitive health state, the PFS HRs applied for abemaciclib plus fulvestrant in the ET-resistant health state, and the efficacy discount rate. However, all resulting NHB results are still positive, indicating that even with the changes conducted within the DSA, ribociclib plus AI remains a cost-effective treatment option vs ET in Population 1 (NATALEE ITT).

Figure 41: DSA tornado diagram for ribociclib plus AI vs ET in Population 1 (NATALEE ITT)

Abbreviations: Abema: abemaciclib; AI: aromatase inhibitor; DSA: deterministic sensitivity analysis; DR: distant recurrence; ET: endocrine therapy; iDFS: invasive disease-free survival; ITT: intention-to-treat; NHB: net health benefit; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival.

Scenario analysis

Details of and justifications for all scenario analyses conducted are provided in Table 69. The results for all scenario analyses conducted in Population 1 (NATALEE ITT) are presented in Table 74. Across the vast majority of scenario analyses, ribociclib plus AI remained dominant vs ET in Population 1 (NATALEE ITT).

Table 74: Scenario analysis results – Population 1 (NATALEE ITT)

Parameter	Base case	Scenario analysis	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Base case			[redacted]	[redacted]	**Dominant**	**0.644**	**0.602**
iDFS extrapolation (ribociclib plus AI/ET)	Exponential	Log-logistic (R)	[redacted]	[redacted]	Dominant	0.540	0.513
		Gamma (R)	[redacted]	[redacted]	Dominant	0.682	0.627
HR for efficacy of tamoxifen vs AIs	HR: 1.10 (Liao *et al.* [2022])[101]	HR: 1.45 (Janni *et al*. [2023])[140]	[redacted]	[redacted]	Dominant	0.793	0.734
		HR: 1 (Assumption)	[redacted]	[redacted]	Dominant	0.601	0.563
Treatment waning	'Carryover benefit' of a constant treatment effect lasting up to 8 years, after which the treatment effect was modelled to wane, to the point at which the iDFS event rate was equal to general population mortality	Treatment effect assumed constant, and life-long, with no treatment waning	[redacted]	[redacted]	Dominant	0.839	0.750
		Treatment effect assumed constant up to 10 years	[redacted]	[redacted]	Dominant	0.674	0.627
		Treatment effect assumed constant up to 5 years	[redacted]	[redacted]	Dominant	0.589	0.555
		Treatment effect assumed constant up to 5 years, with treatment waning from Years 5–8 only	[redacted]	[redacted]	3,983	0.248	0.268
Efficacy of post-progression therapies in DR health state	ET-resistant MONALEESA-3 OS: Loglogistic (R)	ET-resistant MONALEESA-3 OS: Weibull (R)	[redacted]	[redacted]	1,330	0.541	0.554
	ET-resistant MONALEESA-3 PFS: Lognormal (R)	ET-resistant MONALEESA-3 PFS: Lognormal (U)	[redacted]	[redacted]	Dominant	0.634	0.595

	ET-resistant MONALEESA-3 TTD: Gompertz (R)	ET-resistant MONALEESA-3 TTD: RCS Weibull (R)	[redacted]	[redacted]	Dominant	0.580	0.559
	ET-sensitive MONALEESA-2 OS: Log-logistic	ET-sensitive MONALEESA-2 OS: Gamma	[redacted]	[redacted]	Dominant	0.690	0.639
	ET-sensitive MONALEESA-2 PFS: Lognormal	ET-sensitive MONALEESA-2 PFS: Exponential	[redacted]	[redacted]	Dominant	0.741	0.668
	ET-sensitive MONALEESA-2 TTD: Exponential	ET-sensitive MONALEESA-2 TTD: Weibull	[redacted]	[redacted]	Dominant	0.662	0.614
	Estimated HRs for PFS, OS and TTD for the given comparator vs ribociclib plus fulvestrant, based on published literature (ET-sensitive substate only): For capecitabine: OS HR: 1.32; PFS HR: 1.64; TTD HR: as per PFS	PFS/OS/TTD HRs for capecitabine were assumed equivalent to letrozole/anastrozole	[redacted]	[redacted]	Dominant	0.662	0.592
Treatment mix of AI/ET (iDFS health state)	Aligned to clinical expert estimates for Population 1 from the September 2024 advisory board (see Appendix Q.3). Estimates for proportion of patients receiving goserelin in addition to ribociclib plus AI adjusted based on literature.	iDFS treatment mix of AI (as part of ribociclib plus AI) and the ET comparator based on those estimated by clinical experts for Population 4	[redacted]	[redacted]	Dominant	0.622	0.582
		Proportion of patients receiving goserelin based on the NATALEE trial (ITT population; April 2024 data cut)	[redacted]	[redacted]	Dominant	0.650	0.605
Treatment mix (DR health state)	45% of patients in the ribociclib plus AI arm of the model would receive retreatment with a CDK4/6 inhibitor in the ET-sensitive DR health state	90% of the ribociclib plus AI arms (and abemaciclib plus ET arm in Population 4) received CDK4/6 rechallenge as per ET arm (ET-sensitive DR health state)	[redacted]	[redacted]	Dominant	0.550	0.550
		70% of the ribociclib plus AI arms (and abemaciclib plus ET arm in Population 4) received CDK4/6	[redacted]	[redacted]	Dominant	0.591	0.573

		rechallenge (ET-sensitive DR health state)					
RDI	RDIs for AI (as part of ribociclib plus AI) and ET (including goserelin) derived from the NATALEE trial	RDIs for all ETs (monotherapy and in combination with a CDK4/6 inhibitor), goserelin and zoledronic acid, were assumed to be [redacted].	[redacted]	[redacted]	Dominant	0.644	0.602
Time on treatment extrapolation (AI [as part of ribociclib plus AI] and ET)	Weibull (R)	Gamma (R)	[redacted]	[redacted]	Dominant	0.650	0.608
Maximum duration of treatment (AI/ET)	5 years	7 years	[redacted]	[redacted]	Dominant	0.735	0.663
		10 years	[redacted]	[redacted]	Dominant	0.850	0.740
Health state utility values	iDFS (on-treatment: 0.7620; off-treatment: 0.7367) and NMR (0.6818) health state utility values derived from EQ-5D-5L data collected directly in NATALEE (ITT population) and mapped onto the EQ-5D-3L UK value set using the mapping function developed by Hernández Alava *et al.* (2017)	iDFS and NMR health state utility values based on those used in TA810 (iDFS: 0.782; NMR: 0.760)	[redacted]	[redacted]	Dominant	0.632	0.590

Abbreviations: AE: adverse event; AI: aromatase inhibitor; CDK4/6: cyclin dependent kinase 4/6; DR: distant recurrence; EQ-5D: EuroQoL-5dimensions; ET: endocrine therapy; HR: hazard ratio; iDFS: invasive disease-free survival; ITT: intention-to-treat; MAIC: matching-adjusted indirect comparison; NICE: National Institute for Health and Care Excellence; NMR: non-metastatic recurrence; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; R: restricted; RCS: restricted cubic spline; RDI: relative dose intensity; TA: technology appraisal; TTD: time-to-treatment discontinuation; U: unrestricted.

B.3.12 Subgroup analysis

B.3.12.1 Population 2 (NATALEE node-positive high-risk)

Deterministic subgroup economic analysis results for ribociclib plus AI vs ET in Population 2 (NATALEE node-positive high-risk) are presented in Table 75 (ICER) and Table 76 (net health benefit).

In the deterministic subgroup economic analysis in Population 2 (NATALEE node-positive high-risk), ribociclib plus AI (with the PAS for ribociclib) was associated with [redacted] more QALYs and reduced total costs of [redacted] vs ET, resulting in ribociclib plus AI dominating ET. NHB results at both a £20,000 and £30,000 WTP threshold are positive, indicating ribociclib plus AI represents a cost-effective use of NHS resources vs ET in Population 2 (NATALEE node-positive high-risk).

Table 75: Deterministic subgroup analysis results: ribociclib plus AI vs ET – Population 2 (NATALEE node-positive high-risk)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ET	[redacted]	14.90	[redacted]				
Ribociclib plus AI	[redacted]	15.51	[redacted]	[redacted]	0.61	[redacted]	Dominant

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gained; QALYs: quality-adjusted life years.

Table 76: Deterministic net health benefit results: ribociclib plus AI vs ET – Population 2 (NATALEE node-positive high-risk)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	NHB at £20,000	NHB at £30,000
ET	[redacted]	[redacted]				
Ribociclib plus AI	[redacted]	[redacted]	[redacted]	[redacted]	0.65	0.60

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; Incr: incremental; LYG: life years gained; QALYs: quality-adjusted life years; NHB: net health benefit.

An ICER convergence plot for the PSA in Population 2 (NATALEE node-positive high-risk) presented in Figure 42 below which demonstrate that the cumulative ICER stabilised after approximately 800 iterations.

Figure 42: ICER convergence plot for the PSA in Population 2 (NATALEE node-positive high-risk)

Abbreviations: ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Probabilistic results for the subgroup economic analysis of ribociclib plus AI vs ET in Population 2 (NATALEE node-positive high-risk) are presented in Table 72 (ICER) and Table 73 (net health benefit).

In the probabilistic subgroup economic analysis for Population 2 (NATALEE node-positive high-risk), ribociclib plus AI (with the PAS for ribociclib) was associated with [redacted] more quality-adjusted life years (QALYs) and decreased total costs of [redacted] in comparison to ET, resulting in ribociclib plus AI dominating ET in this population (Table 77). NHB results at both a £20,000 and £30,000 willingness-to-pay (WTP) threshold are positive, indicating ribociclib plus AI represents a cost-effective use of NHS resources vs ET in Population 2 (NATALEE node-positive high-risk).

Table 77: Probabilistic subgroup analysis results: ribociclib plus AI vs ET – Population 2 (NATALEE node-positive high-risk)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ET	[redacted]	14.97	[redacted]				
Ribociclib plus AI	[redacted]	15.57	[redacted]	[redacted]	0.60	[redacted]	Dominant

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gained; QALYs: quality-adjusted life years.

Table 78: Probabilistic NHB results: ribociclib plus AI vs ET – Population 2 (NATALEE node-positive high-risk)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	NHB at £20,000	NHB at £30,000
ET	[redacted]	[redacted]				
Ribociclib plus AI	[redacted]	[redacted]	[redacted]	[redacted]	0.64	0.59

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; Incr: incremental; LYG: life years gained; QALYs: quality-adjusted life years; NHB: net health benefit.

A scatter plot showing the incremental costs and QALYs from the 1,000 iterations of the PSA for ribociclib plus AI vs ET in Population 2 (NATALEE node-positive high-risk) is presented in Figure 43, and indicates a [redacted] and [redacted] likelihood of ribociclib plus AI being cost-effective vs ET at WTP thresholds of £20,000 and £30,000 per QALY gained, respectively.

Figure 43: PSA scatter plot for ribociclib plus AI vs ET – Population 2 (NATALEE node-positive high-risk)

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years; WTP: willingness to pay.

The CEAC for ribociclib plus AI vs ET in Population 2 (NATALEE node-positive high-risk) are presented in Figure 44.

Figure 44: CEAC for ribociclib plus AI vs ET – Population 2 (NATALEE node-positive high-risk)

Abbreviations: AI: aromatase inhibitor; CEAC: cost-effectiveness acceptability curve; ET: endocrine therapy; QALY: quality-adjusted life year; ribo: ribociclib; WTP: willingness to pay

Deterministic sensitivity analysis

DSA was undertaken to explore the impact of changing key model parameter values on the NHB. Parameters were varied by +/- 10% in order to assess the relative impact of these parameters on the cost-effectiveness estimates.

The tornado diagram showing the key drivers of the DSA in the economic subgroup analysis of ribociclib plus AI vs ET in Population 2 (NATALEE node-positive high-risk) is presented in Figure 45. The largest model drivers were the PFS HRs applied for capecitabine in the ET-sensitive DR health state, the PFS HRs applied for abemaciclib plus fulvestrant in the ET-resistant DR health state and the OS HRs applied for capecitabine in the ET-resistant DR health state. However, all resulting NHB results are still positive, indicating that even with the changes conducted within the DSA, ribociclib plus AI remains a cost-effective treatment option vs ET in Population 2 (NATALEE node-positive high-risk).

Figure 45: DSA tornado diagram for ribociclib plus AI vs ET in Population 2 (NATALEE node-positive high-risk)

Abbreviations: Abema: abemaciclib; AI: aromatase inhibitor; DSA: deterministic sensitivity analysis; DR: distant recurrence; ET: endocrine therapy; iDFS: invasive disease-free survival; NHB: net health benefit; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; Ribo: ribociclib.

Scenario analyses

Details of and justifications for all scenario analyses conducted are provided in Table 69. The results for all scenario analyses conducted in Population 2 (NATALEE node-positive high-risk) are presented in Table 79. Across the vast majority of scenario analyses, ribociclib plus AI remained dominant vs ET in Population 2 (NATALEE node-positive high-risk).

Table 79: Scenario analysis results – Population 2 (NATALEE node-positive high-risk)

Parameter	Base case	Scenario analysis	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Base case			[redacted]	[redacted]	Dominant	0.651	0.600
iDFS extrapolation (ribociclib plus AI/ET)	Exponential	Gamma (U)	[redacted]	[redacted]	Dominant	0.606	0.553
		Weibull (U)	[redacted]	[redacted]	Dominant	0.620	0.564
HR for efficacy of tamoxifen vs AIs	HR: 1.10 (Liao *et al.* [2022])[101]	HR: 1.45 (Janni *et al.* [2023])[140]	[redacted]	[redacted]	Dominant	0.805	0.736
		HR: 1 (Assumption)	[redacted]	[redacted]	Dominant	0.607	0.560
Treatment waning	'Carryover benefit' of a constant treatment effect lasting up to 8 years, after which the treatment effect was modelled to wane, to the point at which the iDFS event rate was equal to general population mortality	Treatment effect assumed constant, and life-long, with no treatment waning	[redacted]	[redacted]	Dominant	0.829	0.735
		Treatment effect assumed constant up to 10 years	[redacted]	[redacted]	Dominant	0.680	0.624
		Treatment effect assumed constant up to 5 years	[redacted]	[redacted]	Dominant	0.600	0.556
		Treatment effect assumed constant up to 5 years, with treatment waning from Years 5–8 only	[redacted]	[redacted]	2,365	0.259	0.271
Efficacy of post-progression therapies in	ET-resistant MONALEESA-3 OS: Loglogistic(R)	ET-resistant MONALEESA-3 OS: Weibull (R)	[redacted]	[redacted]	629	0.543	0.549
	ET-resistant MONALEESA-3 PFS: Lognormal (R)	ET-resistant MONALEESA-3 PFS: Lognormal (U)	[redacted]	[redacted]	Dominant	0.642	0.593

Parameter	Base case	Scenario analysis	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
DR health state	ET-resistant MONALEESA-3 TTD: Gompertz (R)	ET-resistant MONALEESA-3 TTD: RCS Weibull (R)	[redacted]	[redacted]	Dominant	0.585	0.556
	ET-sensitive MONALEESA-2 OS: Log-logistic	ET-sensitive MONALEESA-2 OS: Gamma	[redacted]	[redacted]	Dominant	0.699	0.639
	ET-sensitive MONALEESA-2 PFS: Lognormal	ET-sensitive MONALEESA-2 PFS: Exponential	[redacted]	[redacted]	Dominant	0.751	0.668
	ET-sensitive MONALEESA-2 TTD: Exponential	ET-sensitive MONALEESA-2 TTD: Weibull	[redacted]	[redacted]	Dominant	0.670	0.613
	Estimated HRs for PFS, OS and TTD for the given comparator vs ribociclib plus fulvestrant, based on published literature: For capecitabine in ET-sensitive: OS HR: 1.32; PFS HR: 1.64; TTD HR: as per PFS	PFS/OS/TTD HRs for capecitabine were assumed equivalent to letrozole/anastrozole	[redacted]	[redacted]	Dominant	0.671	0.590
Treatment mix of AI/ET (iDFS health state)	Aligned to clinical expert estimates for Population 1 from the September 2024 advisory board (see Appendix Q.3). Estimates for proportion of patients receiving goserelin in addition to ribociclib plus AI adjusted based on literature.	iDFS treatment mix of AI (as part of ribociclib plus AI) and the ET comparator based on those estimated by clinical experts for Population 4	[redacted]	[redacted]	Dominant	0.629	0.580
		Proportion of patients receiving goserelin based on the NATALEE trial (ITT population; April 2024 data cut)	[redacted]	[redacted]	Dominant	0.657	0.604
Treatment mix (DR health state)	45% of patients in the ribociclib plus AI arm of the model would receive retreatment with a CDK4/6 inhibitor in the ET-sensitive DR health state	90% of the ribociclib plus AI arms (and abemaciclib plus ET arm in Population 4) received CDK4/6 rechallenge as per ET arm (ET-sensitive DR health state)	[redacted]	[redacted]	Dominant	0.554	0.546
		70% of the ribociclib plus AI arms (and abemaciclib plus ET arm in Population	[redacted]	[redacted]	Dominant	0.597	0.570

Parameter	Base case	Scenario analysis	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
		4) received CDK4/6 rechallenge (ET-sensitive DR health state)					
RDI	Same RDIs for AI (as part of ribociclib plus AI) and ET were assumed as per Population 1.	RDIs for all ETs (monotherapy and in combination with a CDK4/6 inhibitor), goserelin and zoledronic acid, were assumed to be [redacted].	[redacted]	[redacted]	Dominant	0.652	0.600
Time on treatment extrapolation (AI [as part of ribociclib plus AI] and ET)	Weibull (R)	Loglogistic (R)	[redacted]	[redacted]	Dominant	0.856	0.801
Maximum duration of treatment (AI/ET)	5 years	7 years	[redacted]	[redacted]	Dominant	0.747	0.665
		10 years	[redacted]	[redacted]	Dominant	0.867	0.745
Health state utility values	iDFS (on-treatment: 0.7620; off-treatment: 0.7367) and NMR (0.6818) health state utility values derived from EQ-5D data collected directly in NATALEE (ITT population)	iDFS and NMR health state utility values based on those used in TA810 (iDFS: 0.782; NMR: 0.760)	[redacted]	[redacted]	Dominant	0.636	0.585

Abbreviations: AE: adverse event; AI: aromatase inhibitor; CDK4/6: cyclin dependent kinase 4/6; DR: distant recurrence; EQ-5D: EuroQoL-5dimensions; ET: endocrine therapy; HR: hazard ratio; iDFS: invasive disease-free survival; Incr: incremental; ITT: intention-to-treat; MAIC: matching-adjusted indirect comparison; NICE: National Institute for Health and Care Excellence; NMR: non-metastatic recurrence; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; (R): restricted; RCS: restricted cubic spline; RDI: relative dose intensity; TA: technology appraisal; TTD: time-to-treatment discontinuation; (U): unrestricted.

B.3.12.2 Population 3 (NATALEE node-negative high-risk)

Deterministic subgroup economic analysis results for ribociclib plus AI vs ET in Population 3 (NATALEE node-negative high-risk) are presented in Table 80 (ICER) and Table 72 (net health benefit).

In the deterministic subgroup economic analysis in Population 3 (NATALEE node-negative high-risk), ribociclib plus AI (with the PAS for ribociclib) was associated with [redacted] more QALYs and reduced total costs of [redacted] vs ET, respectively, resulting in ribociclib plus AI dominating ET. NHB results at both a £20,000 and £30,000 WTP threshold are positive, indicating ribociclib plus AI represents a cost-effective use of NHS resources vs ET in Population 3 (NATALEE node-negative high-risk).

Table 80: Deterministic subgroup analysis results: ribociclib plus AI vs ET – Population 3 (NATALEE node-negative high-risk)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ET	[redacted]	14.75	[redacted]				
Ribociclib plus AI	[redacted]	15.54	[redacted]	[redacted]	0.79	[redacted]	Dominant

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gained; QALYs: quality-adjusted life years.

Table 81: Deterministic net health benefit results: ribociclib plus AI vs ET – Population 3 (NATALEE node-negative high-risk)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	NHB at £20,000	NHB at £30,000
ET	[redacted]	[redacted]				
Ribociclib plus AI	[redacted]	[redacted]	[redacted]	[redacted]	0.70	0.67

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; Incr: incremental; LYG: life years gained; QALYs: quality-adjusted life years; NHB: net health benefit.

An ICER convergence plot for the PSA in Population 3 (NATALEE node-negative high-risk) presented in Figure 42 below which demonstrate that the cumulative ICER stabilised after approximately 500 iterations.

Figure 46: ICER convergence plot for the PSA in Population 3 (NATALEE node-negative high-risk)

Abbreviations: ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Probabilistic results for the subgroup economic analysis of ribociclib plus AI vs ET in Population 3 (NATALEE node-negative high-risk) are presented in Table 82 (ICER) and Table 83 (net health benefit).

In the probabilistic subgroup economic analysis for Population 3 (NATALEE node-negative high-risk), ribociclib plus AI (with the PAS for ribociclib) was associated with [redacted] more quality-adjusted life years (QALYs) and decreased total costs of [redacted] in comparison to ET, resulting in ribociclib plus AI dominating ET in this population (Table 70). NHB results at both a £20,000 and £30,000 WTP threshold are positive, indicating ribociclib plus AI represents a cost-effective use of NHS resources vs ET in Population 3 (NATALEE node-negative high-risk).

Table 82: Probabilistic base case results: ribociclib plus AI vs ET – Population 3 (NATALEE node-negative high-risk)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ET	[redacted]	14.85	[redacted]				
Ribociclib plus AI	[redacted]	15.45	[redacted]	[redacted]	0.60	[redacted]	Dominant

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gained; QALYs: quality-adjusted life years.

Table 83: Probabilistic NHB results: ribociclib plus AI vs ET – Population 3 (NATALEE node-negative high-risk)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	NHB at £20,000	NHB at £30,000

ET	[redacted]	[redacted]				
Ribociclib plus AI	[redacted]	[redacted]	[redacted]	[redacted]	0.51	0.50

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; Incr: incremental; LYG: life years gained; QALYs: quality-adjusted life years; NHB: net health benefit.

A scatter plot showing the incremental costs and QALYs from the 1,000 iterations of the PSA for ribociclib plus AI vs ET in Population 3 (NATALEE node-negative high-risk) is presented in Figure 47, and indicates a [redacted] and [redacted] likelihood of ribociclib plus AI being cost-effective vs ET at WTP thresholds of £20,000 and £30,000 per QALY gained, respectively.

Figure 47: PSA scatter plot for ribociclib plus AI vs ET – Population 3 (NATALEE node-negative high-risk)

[redacted]

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years; WTP: willingness to pay.

The CEAC for ribociclib plus AI vs ET in Population 3 (NATALEE node-negative high-risk) are presented in Figure 48.

Figure 48: CEAC for ribociclib plus AI vs ET – Population 3 (NATALEE node-negative high-risk)

Abbreviations: AI: aromatase inhibitor; CEAC: cost-effectiveness acceptability curve; ET: endocrine therapy; QALY: quality-adjusted life year; ribo: ribociclib; WTP: willingness to pay.

Deterministic sensitivity analysis

DSA was undertaken to explore the impact of changing key model parameter values on the NHB. Parameters were varied by +/- 10% in order to assess the relative impact of these parameters on the cost-effectiveness estimates.

The tornado diagram showing the key drivers of the DSA in the economic analysis of ribociclib plus AI vs ET in Population 3 (NATALEE node-negative high-risk) is presented in Figure 49. The largest model drivers were the clinical efficacy discount rate, the PFS HRs applied for capecitabine in the ET-sensitive DR health state, and the PFS HRs applied for abemaciclib plus fulvestrant in the ET-resistant DR health state . However, all resulting NHB results are still positive, indicating that even with the changes conducted within the DSA, ribociclib plus AI remains a cost-effective treatment option vs ET in Population 3 (NATALEE node-negative high-risk).

Figure 49: DSA tornado diagram for ribociclib plus AI vs ET in Population 3 (NATALEE node-negative high-risk)

Abbreviations: Abema: abemaciclib; AI: aromatase inhibitor; DSA: deterministic sensitivity analysis; DR: distant recurrence; ET: endocrine therapy; iDFS: invasive disease-free survival; NHB: net health benefit; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; Ribo: ribociclib.

Scenario analyses

Details of and justifications for all scenario analyses conducted are provided in Table 69. The results for all scenario analyses conducted in Population 3 (NATALEE node-negative high-risk) are presented in Table 84. Across the vast majority of scenario analyses, ribociclib plus AI remained dominant vs ET in Population 3 (NATALEE node-negative high-risk).

Table 84: Scenario analysis results – Population 3 (NATALEE node-negative high-risk)

Parameter	Base case	Scenario analysis	In. costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Base case			[redacted]	[redacted]	Dominant	0.700	0.669
iDFS extrapolation (ribociclib plus AI/ET)	RCS log-logistic (U)	Generalised gamma (U)	[redacted]	[redacted]	Dominant	0.551	0.550
		Generalised F (U)	[redacted]	[redacted]	1,394	0.486	0.498
HR for efficacy of tamoxifen vs Ais	HR: 1.10 (Liao *et al.* [2022])[101]	HR: 1.45 (Janni *et al*. [2023])[140]	[redacted]	[redacted]	Dominant	0.832	0.786
		HR: 1 (Assumption)	[redacted]	[redacted]	Dominant	0.662	0.636
Treatment waning	'Carryover benefit' of a constant treatment effect lasting up to 8 years, after which the treatment effect was modelled to wane, to the point at which the iDFS event rate was equal to general population mortality	Treatment effect assumed constant, and life-long, with no treatment waning	[redacted]	[redacted]	Dominant	0.905	0.821
		Treatment effect assumed constant up to 10 years	[redacted]	[redacted]	Dominant	0.737	0.700
		Treatment effect assumed constant up to 5 years	[redacted]	[redacted]	Dominant	0.633	0.615
		Treatment effect assumed constant up to 5 years, with treatment waning from Years 5–8 only	[redacted]	[redacted]	8,752	0.211	0.266
Efficacy of post-progression therapies in DR health state	ET-resistant MONALEESA-3 OS: Loglogistic (R)	ET-resistant MONALEESA-3 OS: Weibull (R)	[redacted]	[redacted]	1,320	0.627	0.641
	ET-resistant MONALEESA-3 PFS : Lognormal (R)	ET-resistant MONALEESA-3 PFS : Lognormal (U)	[redacted]	[redacted]	Dominant	0.692	0.664

Parameter	Base case	Scenario analysis	In. costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
	ET-resistant MONALEESA-3 TTD : Gompertz (R)	ET-resistant MONALEESA-3 TTD: RCS Weibull (R)	[redacted]	[redacted]	Dominant	0.651	0.637
	ET-sensitive MONALEESA-2 OS : Log-logistic	ET-sensitive MONALEESA-2 OS: Gamma	[redacted]	[redacted]	Dominant	0.737	0.704
	ET-sensitive MONALEESA-2 PFS : Lognormal	ET-sensitive MONALEESA-2 PFS : Exponential	[redacted]	[redacted]	Dominant	0.794	0.734
	ET-sensitive MONALEESA-2 TTD: Exponential	ET-sensitive MONALEESA-2 TTD: Weibull	[redacted]	[redacted]	Dominant	0.717	0.681
	Estimated HRs for PFS, OS and TTD for the given comparator vs ribociclib plus fulvestrant, based on published literature (ET-sensitive substate only): For capecitabine: OS HR: 1.32; PFS HR: 1.64; TTD HR: as per PFS	PFS/OS/TTD HRs for capecitabine were assumed equivalent to letrozole/anastrozole	[redacted]	[redacted]	Dominant	0.714	0.663
Treatment mix of AI/ET (iDFS health state)	Aligned to clinical expert estimates for Population 1 from the September 2024 advisory board (see Appendix Q.3). Estimates for proportion of patients receiving goserelin in addition to ribociclib plus AI adjusted based on literature.	iDFS treatment mix of AI (as part of ribociclib plus AI) and the ET comparator based on those estimated by clinical experts for Population 4	[redacted]	[redacted]	Dominant	0.680	0.652
		Proportion of patients receiving goserelin based on the NATALEE trial (ITT population; April 2024 data cut)	[redacted]	[redacted]	Dominant	0.706	0.673

Parameter	Base case	Scenario analysis	In. costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Treatment mix (DR health state)	45% of patients in the ribociclib plus AI arm of the model would receive retreatment with a CDK4/6 inhibitor in the ET-sensitive DR health state	90% of the ribociclib plus AI arms (and abemaciclib plus ET arm in Population 4) received CDK4/6 rechallenge as per ET arm (ET-sensitive DR health state)	[redacted]	[redacted]	150	0.628	0.630
		70% of the ribociclib plus AI arms (and abemaciclib plus ET arm in Population 4) received CDK4/6 rechallenge (ET-sensitive DR health state)	[redacted]	[redacted]	Dominant	0.660	0.647
RDI	Same RDIs for AI (as part of ribociclib plus AI) and ET were assumed as per Population 1.	RDIs for all ETs (monotherapy and in combination with a CDK4/6 inhibitor), goserelin and zoledronic acid, were assumed to be [redacted].	[redacted]	[redacted]	Dominant	0.700	0.670
Time on treatment extrapolation (AI [as part of ribociclib plus AI] and ET)	Gamma (R)	Weibull (R)	[redacted]	[redacted]	Dominant	0.695	0.664
Maximum duration of treatment (AI/ET)	5 years	7 years	[redacted]	[redacted]	Dominant	0.776	0.724
		10 years	[redacted]	[redacted]	Dominant	0.875	0.793
Health state utility values	iDFS (on-treatment: 0.7620; off-treatment: 0.7367) and NMR (0.6818) health state utility values derived from EQ-5D data collected directly in NATALEE (ITT population)	iDFS and NMR health state utility values based on those used in TA810 (iDFS: 0.782; NMR: 0.760)	[redacted]	[redacted]	Dominant	0.703	0.673

Abbreviations: AE: adverse event; AI: aromatase inhibitor; CDK4/6: cyclin dependent kinase 4/6; DR: distant recurrence; EQ-5D: EuroQoL-5dimensions; ET: endocrine therapy; HR: hazard ratio; iDFS: invasive disease-free survival; Incr: incremental; ITT: intention-to-treat; MAIC: matching-adjusted indirect comparison; NICE: National Institute for Health and Care Excellence; NMR: non-metastatic recurrence; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; RCS: restricted cubic spline; RDI: relative dose intensity; TA: technology appraisal; TTD: time-to-treatment discontinuation; (U): unrestricted.

B.3.12.3 Population 4 (node-positive high-risk eligible for abemaciclib)

Deterministic subgroup economic analysis results for ribociclib plus AI vs abemaciclib plus ET and ET in Population 4 (node-positive high-risk eligible for abemaciclib) are presented in Table 85 (ICER) and Table 86 (net health benefit).

In the deterministic subgroup economic analysis in Population 4 (node-positive high-risk eligible for abemaciclib), ribociclib plus AI (with the PAS for ribociclib) was associated with [redacted] more QALYs and reduced total costs of [redacted] vs ET, resulting in ribociclib plus AI dominating ET. Additionally, ribociclib plus AI (with the PAS for ribociclib) was associated with [redacted] more QALYs and reduced total costs of [redacted] vs abemaciclib plus ET, resulting in ribociclib plus AI dominating abemaciclib plus ET. NHB results at both a £20,000 and £30,000 WTP threshold are positive, indicating ribociclib plus AI represents a cost-effective use of NHS resources vs ET and abemaciclib plus ET in Population 4 (node-positive high-risk eligible for abemaciclib).

Table 85: Deterministic subgroup analysis results (incremental analysis): ribociclib plus AI vs ET and abemaciclib plus ET – Population 4 (node-positive high-risk eligible for abemaciclib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Ribociclib plus AI	[redacted]	15.19	[redacted]				
ET	[redacted]	14.51	[redacted]	[redacted]	–0.68	[redacted]	Dominated
Abemaciclib plus ET	[redacted]	15.19	[redacted]	[redacted]	0.00	[redacted]	Dominated

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gained; QALYs: quality-adjusted life years.

Table 86: Net health benefit results: ribociclib plus AI vs ET and abemaciclib plus ET – Population 4 (node-positive high-risk eligible for abemaciclib)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	NHB at £20,000	NHB at £30,000
Ribociclib plus AI	[redacted]	[redacted]				
ET	[redacted]	[redacted]	[redacted]	[redacted]	0.66	0.61
Abemaciclib plus ET	[redacted]	[redacted]	[redacted]	[redacted]	1.97	1.31

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; Incr: incremental; LYG: life years gained; QALYs: quality-adjusted life years; NHB: net health benefit.

An ICER convergence plot for the PSA for ribociclib plus AI vs ET in Population 4 (node-positive high-risk eligible for abemaciclib) is presented in Figure 50 below which demonstrate that the cumulative ICER stabilised after approximately 800 iterations.

Figure 50: ICER convergence plot for the PSA for ribociclib plus AI vs ET in Population 4 (node-positive high-risk eligible for abemaciclib)

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

An ICER convergence plot for the PSA for ribociclib plus AI vs abemaciclib plus ET in Population 4 (node-positive high-risk eligible for abemaciclib) is presented in Figure 51 below which demonstrate that the cumulative ICER stabilised after approximately 500 iterations.

Figure 51: ICER convergence plot for the PSA for ribociclib plus AI vs abemaciclib plus ET in Population 4 (node-positive high-risk eligible for abemaciclib)

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Probabilistic results for the subgroup economic analysis of ribociclib plus AI vs ET and abemaciclib plus ET in Population 4 (node-positive high-risk eligible for abemaciclib) are presented in Table 87 (ICER) and Table 88 (net health benefit).

In the probabilistic subgroup economic analysis in Population 4 (node-positive high-risk eligible for abemaciclib), ribociclib plus AI (with the PAS for ribociclib) was associated with [redacted] more QALYs and decreased total costs of [redacted] in comparison to ET, resulting in ribociclib plus AI dominating ET in this population. Additionally, ribociclib plus AI (with the PAS for ribociclib) was associated with [redacted] more QALYs and decreased total costs of [redacted] in comparison to abemaciclib plus ET, resulting in ribociclib plus AI dominating abemaciclib plus ET in this population (Table 87).

NHB results at both a £20,000 and £30,000 willingness-to-pay (WTP) threshold are positive, indicating ribociclib plus AI represents a cost-effective use of NHS resources vs abemaciclib plus ET and ET in Population 4 (node-positive high-risk eligible for abemaciclib).

Table 87: Probabilistic base case results: ribociclib plus AI vs ET and abemaciclib plus ET – Population 4 (node-positive high-risk eligible for abemaciclib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Ribociclib plus AI	[redacted]	15.26	[redacted]				
ET	[redacted]	14.59	[redacted]	[redacted]	–0.67	[redacted]	Dominated

Abemaciclib plus ET	[redacted]	15.26	[redacted]	[redacted]	0.00	[redacted]	Dominated

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gained; QALYs: quality-adjusted life years.

Table 88: Probabilistic NHB results: ribociclib plus AI vs ET and abemaciclib plus ET – Population 4 (node-positive high-risk eligible for abemaciclib)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	NHB at £20,000	NHB at £30,000
Ribociclib plus AI	[redacted]	[redacted]				
ET	[redacted]	[redacted]	[redacted]	[redacted]	0.64	0.60
Abemaciclib plus ET	[redacted]	[redacted]	[redacted]	[redacted]	1.92	1.28

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; Incr: incremental; ITT: intention to treat; LYG: life years gained; QALYs: quality-adjusted life years; NHB: net health benefit.

Scatter plots showing the incremental costs and QALYs from the 1,000 iterations of the PSA for ribociclib plus AI vs ET and abemaciclib plus ET in Population 4 (node-positive high-risk eligible for abemaciclib) are presented in Figure 52 and Figure 53, respectively. Figure 52 indicates a [redacted] and [redacted] likelihood of ribociclib plus AI being cost-effective vs ET at WTP thresholds of £20,000 and £30,000 per QALY gained, respectively. Figure 53 indicates a [redacted] likelihood of ribociclib plus AI being cost-effective vs abemaciclib plus ET at both WTP thresholds of £20,000 and £30,000 per QALY gained.

Figure 52: PSA scatter plot for ribociclib plus AI vs ET – Population 4 (node-positive high-risk eligible for abemaciclib)

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years; WTP: willingness to pay.

Figure 53: PSA scatter plot for ribociclib plus AI vs abemaciclib plus ET – Population 4 (node-positive high-risk eligible for abemaciclib)

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years; WTP: willingness to pay.

The CEAC for ribociclib plus AI vs ET, and ribociclib plus AI vs abemaciclib plus ET in Population 4 (node-positive high-risk eligible for abemaciclib) are presented in Figure 54.

Figure 54: CEAC for ribociclib plus AI vs ET, and vs abemaciclib plus ET – Population 4 (node-positive high-risk eligible for abemaciclib)

Abbreviations: Abe: abemaciclib; AI: aromatase inhibitor; CEAC: cost-effectiveness acceptability curve; ET: endocrine therapy; QALY: quality-adjusted life year; ribo: ribociclib; WTP: willingness to pay.

Deterministic sensitivity analysis

DSA was undertaken to explore the impact of changing key model parameter values on the NHB. Parameters were varied by +/- 10% in order to assess the relative impact of these parameters on

the cost-effectiveness estimates.

The tornado diagrams showing the key drivers of the DSA in the economic analysis of ribociclib plus AI vs ET and abemaciclib plus ET in Population 4 (node-positive high-risk eligible for abemaciclib) are presented in Figure 55 and Figure 56, respectively.

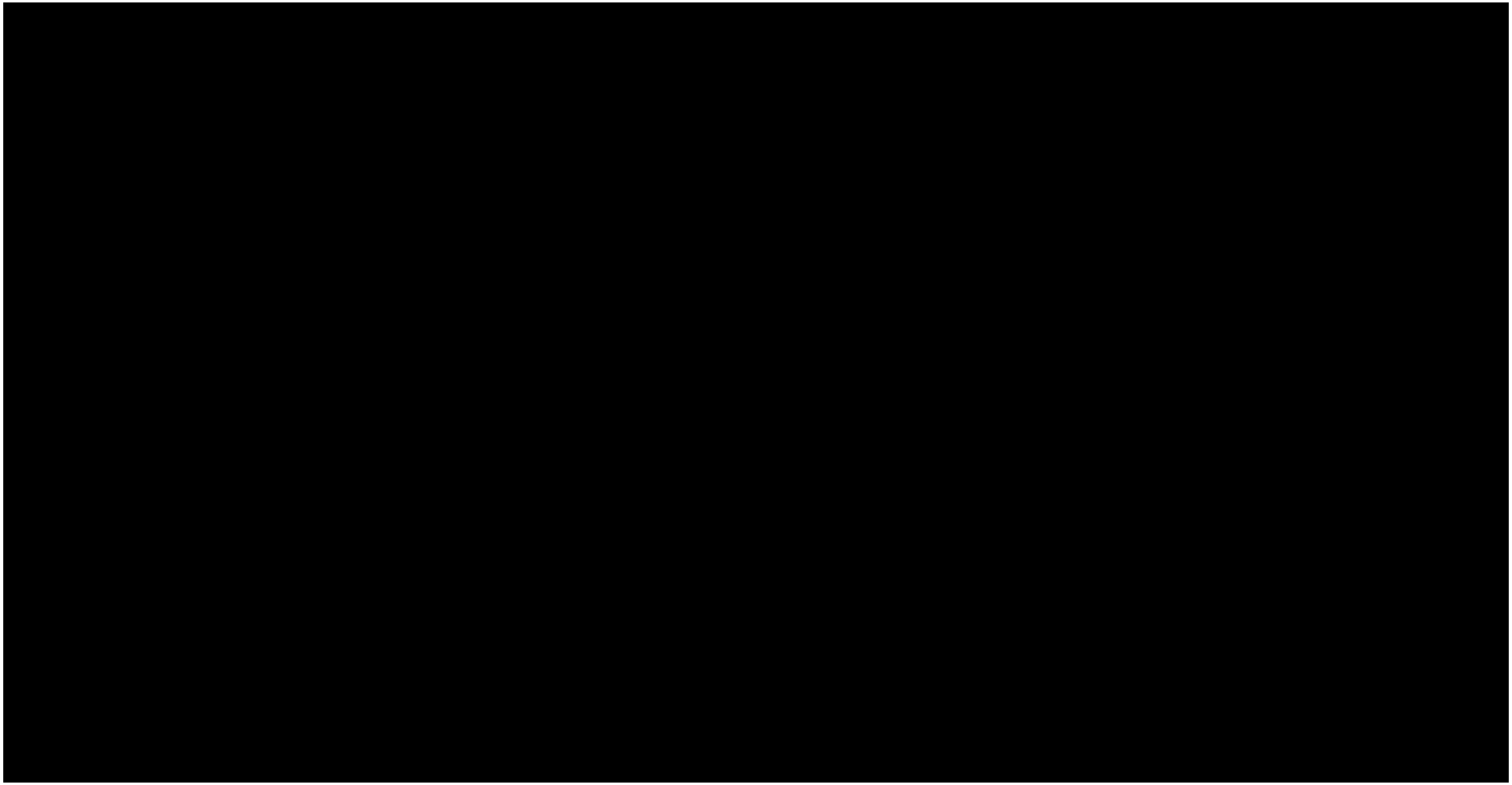
The largest model drivers for the comparison of ribociclib plus AI vs ET were the PFS HRs applied for capecitabine in the ET-sensitive DR health state, the PFS HRs applied for abemaciclib plus fulvestrant in the ET-resistant DR health state, and the OS HRs applied for capecitabine in the ET-resistant DR health state. However, all resulting NHB results are still positive, indicating that even with the changes conducted within the DSA, ribociclib plus AI remains a cost-effective treatment option vs ET in Population 4 node-positive high-risk eligible for abemaciclib).

The largest model drivers for the comparison of ribociclib plus AI vs abemaciclib plus ET were the abemaciclib RDI, the percentage of patients receiving abemaciclib, and the percentage of patients receiving ribociclib. However, all resulting NHB results are still positive, indicating that even with the changes conducted within the DSA, ribociclib plus AI remains a cost-effective treatment option vs abemaciclib plus ET in Population 4 (node-positive high-risk eligible for abemaciclib).

Figure 55: DSA tornado diagram for ribociclib plus AI vs ET in Population 4 (node-positive high-risk eligible for abemaciclib)

Abbreviations: AI: aromatase inhibitor; DSA: deterministic sensitivity analysis; DR: distant recurrence; ET: endocrine therapy; iDFS: invasive disease-free survival; NHB: net health benefit; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; Ribo: ribociclib.

Figure 56: DSA tornado diagram for ribociclib plus AI vs abemaciclib plus ET in Population 4 (node-positive high-risk eligible for abemaciclib)



Abbreviations: Abe: abemaciclib: AI: aromatase inhibitor; DR: distant recurrence; DSA: deterministic sensitivity analysis; ET: endocrine therapy; iDFS: invasive disease-free survival; NHB: net health benefit; RDI: relative dose intensity; Ribo: ribociclib.

Scenario analyses

Details of and justifications for all scenario analyses conducted are provided in Table 69. The results for all scenario analyses conducted in Population 4 (node-positive high-risk eligible for abemaciclib) are presented in Table 89 for ribociclib plus AI vs ET and Table 90 for ribociclib plus AI vs abemaciclib plus ET. Across the vast majority of scenario analyses, ribociclib plus AI remained dominant vs abemaciclib plus ET and ET in Population 4 (node-positive high-risk eligible for abemaciclib).

Table 89: Scenario analysis results vs ET – Population 4 (node-positive high-risk eligible for abemaciclib)

Parameter	Base case	Scenario analysis	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Base case			[redacted]	[redacted]	**Dominant**	**0.657**	**0.611**
iDFS extrapolation (ribociclib plus AI/ET)	Exponential (MAIC)	Gamma (U) (MAIC)	[redacted]	[redacted]	Dominant	0.819	0.755
		Gamma (R) (MAIC)	[redacted]	[redacted]	Dominant	0.655	0.610
Efficacy of tamoxifen vs AIs	HR: 1.10 (Liao *et al.* [2022])[101]	HR: 1.45 (Janni *et al.* [2023])[140]	[redacted]	[redacted]	Dominant	0.735	0.681
		HR: 1 (Assumption)	[redacted]	[redacted]	Dominant	0.634	0.590
Treatment waning	'Carryover benefit' of a constant treatment effect lasting up to 8 years, after which the treatment effect was modelled to wane, to the point at which the iDFS event rate was equal to general population mortality	Treatment effect assumed constant, and life-long, with no treatment waning	[redacted]	[redacted]	Dominant	0.830	0.751
		Treatment effect assumed constant up to 10 years	[redacted]	[redacted]	Dominant	0.685	0.635
		Treatment effect assumed constant up to 5 years	[redacted]	[redacted]	Dominant	0.605	0.565
		Treatment effect assumed constant up to 5 years, with treatment waning from Years 5–8 only	[redacted]	[redacted]	327	0.285	0.287

Efficacy of post-progression therapies in DR health state	ET-resistant ML3 OS: Loglogistic (R)	ET-resistant ML3 OS: Weibull (R)	[redacted]	[redacted]	1,410	0.540	0.554
	ET-resistant ML3 PFS: Lognormal (R)	ET-resistant ML3 PFS: Lognormal (U)	[redacted]	[redacted]	Dominant	0.647	0.604
	ET-resistant ML3 TTD: Gompertz (R)	ET-resistant ML3 TTD: RCS Weibull (R)	[redacted]	[redacted]	Dominant	0.586	0.564
	ET-sensitive ML2 OS: Log-logistic	ET-sensitive ML2 OS: Gamma	[redacted]	[redacted]	Dominant	0.706	0.646
	ET-sensitive ML2 PFS: Lognormal	ET-sensitive ML2 PFS: Exponential	[redacted]	[redacted]	Dominant	0.744	0.671
	ET-sensitive ML2 TTD: Exponential	ET-sensitive ML2 TTD: Weibull	[redacted]	[redacted]	Dominant	0.674	0.622
	Estimated HRs for PFS, OS and TTD in ET-sensitive DR health state for the given comparator vs ribociclib plus fulvestrant, based on published literature: For capecitabine: OS HR: 1.32; PFS HR: 1.64; TTD HR: as per PFS	PFS/OS/TTD HRs for capecitabine were assumed equivalent to letrozole/anastrozole	[redacted]	[redacted]	Dominant	0.679	0.600
Treatment mix of AI/ET (iDFS health state)	Aligned to clinical expert estimates for Population 4 from the September 2024 advisory board (see Appendix Q.3). The proportion of patients receiving goserelin in addition to abemaciclib plus ET in assumed to be equal to the proportion of patients receiving goserelin in addition to ribociclib plus AI.	iDFS treatment mix of AI (as part of ribociclib plus AI), ET (as part of abemaciclib plus ET) and the ET comparator based on those estimated by clinical experts for Population 1. Here, ET (as part of abemaciclib plus ET) was based on the treatment mix of AI as part of ribociclib plus AI) in Population 1	[redacted]	[redacted]	Dominant	0.679	0.631

		Proportion of patients receiving goserelin based on the NATALEE trial (ITT population; April 2024 data cut)	[redacted]	[redacted]	Dominant	0.653	0.608
Treatment mix (DR health state)	45% of patients in the ribociclib plus AI arm of the model would receive retreatment with a CDK4/6 inhibitor in the ET-sensitive DR health state	90% of the ribociclib plus AI arms (and abemaciclib plus ET arm in Population 4) received CDK4/6 rechallenge as per ET arm (ET-sensitive DR health state)	[redacted]	[redacted]	83	0.552	0.553
		70% of the ribociclib plus AI arms (and abemaciclib plus ET arm in Population 4) received CDK4/6 rechallenge (ET-sensitive DR health state)	[redacted]	[redacted]	Dominant	0.599	0.579
RDI	RDI for abemaciclib calculated from RDI data for ribociclib (treatment pauses only) from the NATALEE trial (ITT population; April 2024 data cut). RDIs for ET (as part of abemaciclib plus ET) assumed to be 100%, based on what was assumed in TA810.[6] The RDIs for ribociclib plus AI and ET alone in assumed to be the same as Population 1.	RDIs for all ETs (monotherapy and in combination with a CDK4/6 inhibitor), goserelin and zoledronic acid, were assumed to be [redacted].	[redacted]	[redacted]	Dominant	0.657	0.611
Time on treatment extrapolation (AI [as part of ribociclib plus AI], ET [as part	Lognormal (R)	RCS Lognormal (R)	[redacted]	[redacted]	Dominant	0.658	0.612

of abemaciclib plus ET], and ET)							
Maximum duration of treatment (AI/ET)	5 years	7 years	[redacted]	[redacted]	Dominant	0.760	0.679
		10 years	[redacted]	[redacted]	Dominant	0.890	0.764
Health state utility values	iDFS (on-treatment: 0.7620; off-treatment: 0.7367) and NMR (0.6818) health state utility values derived from EQ-5D data collected directly in NATALEE (ITT population)	iDFS and NMR health state utility values based on those used in TA810 (iDFS: 0.782; NMR: 0.76)	[redacted]	[redacted]	Dominant	0.649	0.604

Abbreviations: AE: adverse event; AI: aromatase inhibitor; CDK4/6: cyclin dependent kinase 4/6; DR: distant recurrence; EQ-5D: EuroQoL-5dimensions; ET: endocrine therapy; HR: hazard ratio; iDFS: invasive disease-free survival; Incr: incremental; ITT: intention-to-treat; MAIC: matching-adjusted indirect comparison; NICE: National Institute for Health and Care Excellence; NMR: non-metastatic recurrence; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; (R): restricted; RCS: restrictied cubic spline; RDI: relative dose intensity; TA: technology appraisal; TTD: time-to-treatment discontinuation; (U): unrestricted.

Table 90: Scenario analysis results vs abemaciclib plus ET – Population 4 (node-positive high-risk eligible for abemaciclib)

Parameter	Base case	Scenario analysis	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Base case			[redacted]	[redacted]	**Dominant**	**1.969**	**1.315**
iDFS extrapolation (ribociclib plus AI/ET)	Exponential (MAIC)	Gamma (U) (MAIC)	[redacted]	[redacted]	Dominant	1.970	1.316
		Gamma (R) (MAIC)	[redacted]	[redacted]	Dominant	1.970	1.315
Efficacy of tamoxifen vs AIs	HR: 1.10 (Liao *et al.* [2022])[101]	HR: 1.45 (Janni *et al.* [2023])[140]	[redacted]	[redacted]	Dominant	1.969	1.315
		HR: 1 (Assumption)	[redacted]	[redacted]	Dominant	1.969	1.315
Treatment waning	'Carryover benefit' of a constant treatment effect lasting up to 8 years, after which the treatment effect	Treatment effect assumed constant, and life-long, with no treatment waning	[redacted]	[redacted]	Dominant	1.970	1.315

	was modelled to wane, to the point at which the iDFS event rate was equal to general population mortality	Treatment effect assumed constant up to 10 years	[redacted]	[redacted]	Dominant	1.970	1.315
		Treatment effect assumed constant up to 5 years	[redacted]	[redacted]	Dominant	1.969	1.314
		Treatment effect assumed constant up to 5 years, with treatment waning from Years 5–8 only	[redacted]	[redacted]	Dominant	1.967	1.312
Efficacy of post-progression therapies in DR health state	ET-resistant ML3 OS: Loglogistic (R)	ET-resistant ML3 OS: Weibull (R)	[redacted]	[redacted]	Dominant	1.969	1.315
	ET-resistant ML3 PFS: Lognormal (R)	ET-resistant ML3 PFS: Lognormal (U)	[redacted]	[redacted]	Dominant	1.969	1.315
	ET-resistant ML3 TTD: Gompertz (R)	ET-resistant ML3 TTD: RCS Weibull (R)	[redacted]	[redacted]	Dominant	1.969	1.315
	ET-sensitive ML2 OS: Log-logistic	ET-sensitive ML2 OS: Gamma	[redacted]	[redacted]	Dominant	1.969	1.315
	ET-sensitive ML2 PFS: Lognormal	ET-sensitive ML2 PFS: Exponential	[redacted]	[redacted]	Dominant	1.969	1.315
	ET-sensitive ML2 TTD: Exponential	ET-sensitive ML2 TTD: Weibull	[redacted]	[redacted]	Dominant	1.969	1.315
	Estimated HRs for PFS, OS and TTD in ET-sensitive DR health state for the given comparator vs ribociclib plus fulvestrant, based on published literature: For capecitabine: OS HR: 1.32; PFS HR: 1.64; TTD HR: as per PFS	PFS/OS/TTD HRs for capecitabine were assumed equivalent to letrozole/anastrozole	[redacted]	[redacted]	Dominant	1.969	1.315

Treatment mix of AI/ET (iDFS health state)	Aligned to clinical expert estimates for Population 4 from the September 2024 advisory board (see Appendix Q.3). The proportion of patients receiving goserelin in addition to abemaciclib plus ET in assumed to be equal to the proportion of patients receiving goserelin in addition to ribociclib plus AI.	iDFS treatment mix of AI (as part of ribociclib plus AI), ET (as part of abemaciclib plus ET) and the ET comparator based on those estimated by clinical experts for Population 1. Here, ET (as part of abemaciclib plus ET) was based on the treatment mix of AI as part of ribociclib plus AI) in Population 1	[redacted]	[redacted]	Dominant	1.969	1.314
		Proportion of patients receiving goserelin based on the NATALEE trial (ITT population; April 2024 data cut)	[redacted]	[redacted]	Dominant	1.930	1.288
Treatment mix (DR health state)	45% of patients in the ribociclib plus AI arm of the model would receive retreatment with a CDK4/6 inhibitor in the ET-sensitive DR health state	90% of the ribociclib plus AI arms (and abemaciclib plus ET arm in Population 4) received CDK4/6 rechallenge as per ET arm (ET-sensitive DR health state)	[redacted]	[redacted]	Dominant	1.969	1.315
		70% of the ribociclib plus AI arms (and abemaciclib plus ET arm in Population 4) received CDK4/6 rechallenge (ET-sensitive DR health state)	[redacted]	[redacted]	Dominant	1.969	1.315
RDI	RDI for abemaciclib calculated from RDI data for ribociclib (treatment pauses only) from the NATALEE trial (ITT	RDIs for all ETs (monotherapy and in combination with a CDK4/6 inhibitor), goserelin and zoledronic	[redacted]	[redacted]	Dominant	1.970	1.315

	population; April 2024 data cut). RDIs for ET (as part of abemaciclib plus ET) assumed to be 100%, based on what was assumed in TA810.[6] The RDIs for ribociclib plus AI and ET alone in assumed to be the same as Population 1.	acid, were assumed to be [redacted].					
		The RDI for abemaciclib assumed to equal the RDI for ribociclib, and the RDIs for ET (as part of abemaciclib plus ET) assumed to equal the RDIs for the relevant AIs in the ribociclib plus AI arm (with tamoxifen and zoledronic acid assumed to be [redacted]	[redacted]	[redacted]	Dominant	1.734	1.158
Time on treatment extrapolation (AI [as part of ribociclib plus AI], ET [as part of abemaciclib plus ET], and ET)	Lognormal (R)	RCS Lognormal (R)	[redacted]	[redacted]	Dominant	1.972	1.317
Time on treatment extrapolation for abemaciclib (as part of abemaciclib plus ET)	Based on KM derived from Rugo *et al.* (2022)[141]	Assumed equal to ribociclib TTD KM from NATALEE high-risk population up to 24 months	[redacted]	[redacted]	7,580,840[a]	1.876	1.249
Maximum duration of treatment (AI/ET)	5 years	7 years	[redacted]	[redacted]	Dominant	1.970	1.315
		10 years	[redacted]	[redacted]	Dominant	1.970	1.315

Health state utility values	iDFS (on-treatment: 0.7620; off-treatment: 0.7367) and NMR (0.6818) health state utility values derived from EQ-5D data collected directly in NATALEE (ITT population)	iDFS and NMR health state utility values based on those used in TA810 (iDFS: 0.782; NMR: 0.76)	[redacted]	[redacted]	Dominant	1.965	1.310

Footnote: [a] This represents the ICER for abemaciclib plus ET vs ribociclib plus AI.
Abbreviations: AE: adverse event; AI: aromatase inhibitor; CDK4/6: cyclin dependent kinase 4/6; DR: distant recurrence; EQ-5D: EuroQoL-5dimensions; ET: endocrine therapy; HR: hazard ratio; iDFS: invasive disease-free survival; Incr: incremental; ITT: intention-to-treat; MAIC: matching-adjusted indirect comparison; NICE: National Institute for Health and Care Excellence; NMR: non-metastatic recurrence; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; (R): restricted; RCS: restricted cubic spline; RDI: relative dose intensity; TA: technology appraisal; TTD: time-to-treatment discontinuation; (U): unrestricted.

B.3.13 Benefits not captured in the QALY calculation

Fear of disease recurrence and the value of hope associated with a new treatment option, particularly among patients who are not eligible for abemaciclib

As discussed in Section B.1.3.5, fear of disease recurrence is a common psychological problem among breast cancer patients and detrimentally impacts psychological wellbeing and overall HRQoL long-term.[22] The impact of this fear amongst patients who remain in breast cancer remission would not be wholly captured by the EQ-5D-5L, and therefore fear of recurrence is a significant consideration that may not be accounted for in these economic analyses.

In the NATALEE trial, ribociclib plus AI was associated with [redacted], clinically meaningful improvements in efficacy compared with AI among patients with HR+/HER2 – EBC at high risk of recurrence (Population 1 (NATALEE ITT). Notably, the iDFS improvement for ribociclib plus AI vs AI was generally consistent across the subgroups of patients (anatomic stage, prior (neo)adjuvant chemotherapy, menopausal status, and geographic region), including across Population 2 (NATALEE high-risk node-positive) and Population 3 (NATALEE high-risk node-negative). The secondary endpoints, including RFS, DDFS were consistent with, and supportive of, the primary endpoint iDFS results; OS results at the April 2024 data cut also indicated an early positive trend in favour of the ribociclib plus AI trial arm of NATALEE.

Importantly, for a large proportion of patients with HR+/HER2– EBC at high risk of recurrence, current adjuvant therapy options are restricted to ET (with or without add-on bisphosphonates), given they are not eligible for abemaciclib plus ET. Specifically, patients with node-negative HR+/HER2– EBC at high risk of recurrence (representing 22.1% of all HR+/HER2– EBC patients at high risk of recurrence) and patients with N1 disease without additional specific anatomical risk factors (representing 33.0% of all HR+/HER2– EBC patients at high risk of recurrence) are not eligible for treatment with abemaciclib plus ET,[7] and therefore the introduction of ribociclib, a orally administered, potent CDK4/6 inhibitor, within these populations would provide a new, promising treatment option. The value of hope associated with introducing a new, effective therapy which reduces disease recurrence (compared with AI) cannot be fully captured in the QALY framework and should therefore be a critical consideration alongside the results of these economic analyses.

Among patients who are currently eligible for abemaciclib in UK clinical practice (i.e., Population 4; node-positive high-risk eligible for abemaciclib), the primary MAIC analysis identified [redacted] in treatment effect in terms of iDFS and OS between ribociclib plus AI and abemaciclib plus ET. The introduction of ribociclib within this population would expand the availability of effective treatment options.

Surgery sparing

Finally, as detailed in Section B.1.3.6 it is the Company's understanding from multiple clinical experts that some patients undergo an additional surgical procedure (ALND) in order to identify additional positive axillary lymph nodes that would qualify them for treatment with adjuvant abemaciclib plus ET.

Specifically, these patients are those with 1-2 positive lymph nodes without any additional high-risk characteristics (tumour size / grade) who would not typically undergo ALND (patients with 3 positive lymph nodes would typically undergo ALND regardless). ALND is associated with

significant morbidity in the form of increased rates of lymphedema, pain, infection, numbness and weakness.

As patients with 1-3 positive ALNs are eligible for ribociclib plus AI, regardless of the presence of additional high-risk characteristics, they would not need to undergo this additional surgical procedure. Were ribociclib plus AI to be made available, this could reduce the need for additional ALND surgery,[80] an aspect that has not been captured within the current economic model.

B.3.14 Validation

B.3.14.1 Validation of cost-effectiveness analysis

Technical validation

Aligned to best practice, an independent health economist validated the economic model structure prior to submission. Quality control procedures, including a technical cell by cell verification of all input data, calculations, data references, model interface, and Visual Basic for Applications code, were also performed. All results generated were checked to ensure accurate and consistent results. The correct functioning of the sensitivity and scenario analyses was also reviewed.

Clinical validation

The Company conducted two advisory boards (November 2023 and September 2024), both with six external UK clinical experts in attendance, to validate the model structure, key inputs and assumptions utilised in the model, including treatment mixes and subsequent treatment choices, treatment efficacy assumptions and survival curve extrapolations (see Appendix Q). In addition, the Company sought independent validation from three clinical experts for the ITCs presented, further strengthening the clinical validity of the analyses conducted (see Appendix Q).

B.3.15 Interpretation and conclusions of economic evidence

The strengths and limitations of the economic evidence presented in this submission are discussed below.

Strengths of the economic evaluation

The principal evidence base informing the economic analyses across all four populations is the NATALEE trial, a large, robust RCT conducted within a broad population of patients with HR+/HER2– EBC at high risk of recurrence (Population 1 [NATALEE ITT]). As confirmed by UK clinical experts, the NATALEE trial can be considered generalisable to patients with HR+/HER2– EBC at high risk of recurrence in the UK (see Appendix Q.2). Given NATALEE was a large trial (N=5,101) which covered a range of high-risk patient populations, it was used to inform iDFS efficacy and TTD across both the base case Population 1 (NATALEE ITT) as well as the three subgroup analyses addressed in this submission (Populations 2–4). Likewise, as NATALEE assessed HRQoL using the EQ-5D, health state utility values used in the model for the majority of health states were derived directly from patients in a generalisable population, in line with the NICE reference case, rather than relying on published utility values from the literature.

At the April 2024 data cut, the median duration of follow-up in NATALEE was [redacted] months, capturing the full duration of treatment with ribociclib, given the maximum treatment duration of ribociclib is 3 years. As the TTD data for ribociclib were therefore mature, TTD for ribociclib

across all four populations was based on the Kaplan-Meier curve for TTD from the NATALEE trial (April 2024 data cut) directly. No parametric distribution extrapolations were necessary which limits the uncertainty associated with this endpoint.

The model structure adopted across all economic evaluations was validated by clinical experts to be appropriate for the decision problem (see Appendix Q.3). The model structure was closely aligned and consistent with model structures identified in the comprehensive SLR on economic evaluations, including model structures used in prior relevant NICE appraisals, such as TA810.[6] However, unlike TA810, the DR substates were modelled via a PSM framework which represents a further strength of the model structure by facilitating the incorporation of mature data from clinical trials for ribociclib in the advanced or metastatic breast cancer setting (MONALEESA-2 for the ET-sensitive substate and MONALEESA-3 for the ET-resistant substate). This approach also enabled more detailed, granular and transparent modelling of QALYs and costs in this health state, compared to alternative approaches.

Finally, a key strength of the economic analyses includes the numerous features that were conducted in line with the NICE reference case, including the time horizon, discount rate, perspective and derivation of health-state utility values using EQ-5D data. Moreover, whilst the model structure is relatively complex to allow for the modelling of four clinically distinct patient populations, this additional complexity has enabled the granular and therefore transparent estimation of the cost-effectiveness of ribociclib plus AI and the full assessment of different forms of uncertainty within each analysis. Where elements of the analysis rely on input from clinical experts, this feedback has been transparently detailed in Appendix Q.

Limitations of the economic evaluation

The NATALEE trial provides comprehensive and robust evidence for the efficacy of ribociclib plus AI vs AI in patients with HR+/HER2– EBC at high risk of recurrence. However, in NATALEE, the starting age of patients in Population 3 (NATALEE node-negative high-risk) was higher ([redacted] years) than patients in the other three populations addressed by this submission (range: [redacted]). This higher starting age results in increased general population mortality rates being applied throughout the model, which serves as both a mortality floor in each model cycle and reduces the treatment waning duration. Consequently, a higher general population mortality rate in this population reduces the total LYs compared to the other three populations included in this submission.

The median duration of follow-up at the latest data cut of NATALEE (April 2024) was [redacted] months. Given the lack of alternative evidence for long-term iDFS for ribociclib plus AI in a population consistent with NATALEE, there is uncertainty regarding the longer-term survival outcomes. Parametric distribution extrapolations for iDFS were therefore used, which, despite curve selection being based on statistical goodness-of-fit, visual fit, and primarily clinical plausibility, remain associated with inherent uncertainty. To explore this uncertainty, scenario analyses were conducted using several alternative iDFS distributions; the results of these scenario analyses demonstrated that iDFS curve selection had minimal impact on resulting ICERs across all populations, with ribociclib plus AI remaining dominant or with ICERs well below the WTP threshold, against the relevant comparators.

Across all economic analyses, iDFS efficacy of the comparator ET was informed by iDFS data for the AI arm of the NATALEE trial. This represents a limitation given the AI arm of the NATALEE trial comprised anastrozole and letrozole, whereas in UK clinical practice, two further ETs

(exemestane and tamoxifen) may also be prescribed. As evidence suggests tamoxifen is less effective than AIs in reducing disease recurrence in EBC (see Appendix M.1), a weighted HR was applied to the AI iDFS curve from NATALEE to reflect any differential efficacy for the proportion of patents receiving these therapies. While the HR for tamoxifen vs AIs used to inform this adjustment was identified via a TLR (see Appendix M.1), uncertainty arising from this assumption remains, and as such, two further scenario analyses were conducted whereby the HR was set to two alternative values. Notably across all four populations, results from these scenario analyses varied minimally from the base case results.

The DR health state was modelled using two PSM frameworks (for the ET-sensitive and ET-resistant DR substates, respectively), with the output of the PSMs (in terms of LYs, QALYs and costs) applied to patients entering the DR health state within the semi-Markov cohort state-transition model. This relies on a number of assumptions, principally the treatment mix and efficacy of subsequent therapies (other than ribociclib) received within the DR health state. Nevertheless, as detailed in in Section B.3.2.2, this approach was taken for a number of reasons and was deemed more granular and therefore more transparent than other methods, for example using a lump-sum approach.

Finally, in the absence of head-to-head data between ribociclib plus AI and abemaciclib plus ET and ET in Population 4 (node-positive high-risk eligible for abemaciclib), iDFS for patients receiving ribociclib plus AI and ET in Population 4 (node-positive high-risk eligible for abemaciclib) was based on parametric survival distributions fit to the matched ribociclib plus AI and AI arms of the NATALEE trial in the NATALEE-selected population. These were derived from the MAIC conducted between NATALEE and Cohort 1 of the monarchE trial (see Section B.2.8) which, despite adjusting for all available baseline characteristics, may still be limited by unreported or unobserved confounding factors. This is an inherent limitation of the MAIC approach.

Summary

Across all four economic analyses, including the base case in Population 1 (NATALEE ITT) and the three economic subgroup analyses in Populations 2–4, ribociclib plus AI was associated with increased QALYs at reduced costs vs ET, hence treatment with ribociclib plus AI vs dominated ET. Also, in Population 4 (node-positive high-risk eligible for abemaciclib), ribociclib plus AI was associated with increased QALYs at reduced costs vs abemaciclib plus ET, hence treatment with ribociclib plus AI dominated abemaciclib plus ET. These results include the PAS for ribociclib and alpelisib, and the list price for all comparators and other treatments, and should therefore be interpreted with caution. Nevertheless, it is expected that when the confidential PAS discounts for abemaciclib and any other treatments are applied, ribociclib plus AI will still represent a cost-effective use of NHS resources across all four populations.

For patients with HR+/HER2– EBC at high risk of recurrence in the UK, including patients with node-positive disease that is eligible for abemaciclib, the introduction of ribociclib plus AI into the treatment pathway is therefore anticipated to provide a new, cost-effective treatment option that is effective in reducing the risk of recurrence, which is critical given the considerably worsened prognoses of patients with HR+/HER2– EBC who experience a disease relapse.

References

1. Novartis. Data on File: Draft Ribociclib SmPc. 2024.
2. Novartis. Data on File: NATALEE Protocol. 2020.
3. European Medicines Agency. Kisqali, INN-ribociclib. Annex I: Summary of Product Characteristics (SmPC). 2017. Available from: https://www.ema.europa.eu/en/documents/product-information/kisqali-epar-product-information_en.pdf. Accessed: 22 October 2024.
4. NICE. Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy [TA687]. 2021. Available from: https://www.nice.org.uk/guidance/TA687. Accessed: 11 October 2024.
5. NICE. Ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer [TA496]. 2017. Available from: https://www.nice.org.uk/guidance/ta496. Accessed: 29 October 2024.
6. NICE. Abemaciclib with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence [TA810]. 2022. Available from: https://www.nice.org.uk/guidance/ta810. Accessed: 11 October 2024.
7. Tarantino P, Rugo HS, Curigliano G, et al. 245P Characteristics of real-world (RW) NATALEE and monarchE eligible populations: A US electronic health records (EHR) database analysis. Annals of Oncology 2024;35:S317-S318.
8. Loibl S, André F, Bachelot T, et al. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of Oncology 2024;35:159-182.
9. Barroso-Sousa R, Shapiro GI, Tolaney SM. Clinical Development of the CDK4/6 Inhibitors Ribociclib and Abemaciclib in Breast Cancer. Breast Care (Basel) 2016;11:167-73.
10. Murphy CG, Dickler MN. The Role of CDK4/6 Inhibition in Breast Cancer. Oncologist 2015;20:483-90.
11. Dewis R, Gribbin J. National Institute for Health and Care Excellence: Guidelines. Breast Cancer: Diagnosis and Treatment: An Assessment of Need. Cardiff (UK): National Collaborating Centre for Cancer (UK) Copyright © 2009, National Collaborating Centre for Cancer, 2009.
12. Finn RS, Dering J, Conklin D, et al. PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro. Breast Cancer Res 2009;11:R77.
13. Miller WR. Aromatase inhibitors: mechanism of action and role in the treatment of breast cancer. Semin Oncol 2003;30:3-11.
14. Braal CL, Jongbloed EM, Wilting SM, et al. Inhibiting CDK4/6 in Breast Cancer with Palbociclib, Ribociclib, and Abemaciclib: Similarities and Differences. Drugs 2021;81:317-331.
15. European Medicines Agency. Ribociclib. Summary of opinion (post authorisation). 2024. Available from: https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-kisqali-ii-45_en.pdf. Accessed 22 October 2024.
16. Cancer Research UK. Breast cancer statistics. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer. Accessed: 18 April 2023.
17. American Cancer Society. Breast Cancer Facts & Figures 2022-2024. 2022. Available from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/2022-2024-breast-cancer-fact-figures-acs.pdf. Accessed: 9 September 2024.
18. Cancer Research UK. Proportion Diagnosed by Stage (stacked chart). 2021 Available from: https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/. Accessed: 7 August 2023.
19. NICE. NG101. Early and locally advanced breast cancer: diagnosis and management. 2018. Available from: https://www.nice.org.uk/guidance/ng101/resources/early-and-locally-advanced-breast-cancer-diagnosis-and-management-pdf-66141532913605. Accessed: April 2023.
20. Pan H, Gray R, Braybrooke J, et al. 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. N Engl J Med 2017;377:1836-1846.
21. Gomis RR, Gawrzak S. Tumor cell dormancy. Mol Oncol 2017;11:62-78.

22. Tran TXM, Jung SY, Lee EG, et al. Fear of Cancer Recurrence and Its Negative Impact on Health-Related Quality of Life in Long-term Breast Cancer Survivors. Cancer Res Treat 2022;54:1065-1073.
23. Komal Jhaveri MP, Patrick Neven, Giuseppe Curigliano, Laura Spring, Joseph Gligorov, Ilana Schlam, Nadia Harbeck, Dejan Juric, Elgene Lim, Shusen Wang, Henry Owusu, Murat Akdere, Fen Ye, Julia Kim, Fatima Cardoso. Real-world evidence on risk of recurrence in patients with node-negative and node-positive HR+/HER2−early breast cancer from US electronic health records. Poster 292P. Presented at European Society for Medical Oncology in Barcenlona, Spain, 13-17 September. 2024.
24. Razavi P, Ahmed M, Roush A, et al. Real-world (RW) risk of recurrence among patients (pts) diagnosed with stage II-III HR+/HER2− early breast cancer (EBC) treated with endocrine therapy (ET) in the US. Journal of Clinical Oncology 2024;42:e12533-e12533.
25. Slamon DJ, Neven P, Chia S, et al. LBA7_PR - Overall survival (OS) results of the phase III MONALEESA-3 trial of postmenopausal patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor 2-negative (HER2−) advanced breast cancer (ABC) treated with fulvestrant (FUL) ± ribociclib (RIB). Annals of Oncology 2019;30:v856-v857.
26. Im SA, Lu YS, Bardia A, et al. Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer. N Engl J Med 2019;381:307-316.
27. Hortobagyi GN, Stemmer S, Burris HA, et al. LBA17 Overall survival (OS) results from the phase III MONALEESA-2 (ML-2) trial of postmenopausal patients (pts) with hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2−) advanced breast cancer (ABC) treated with endocrine therapy (ET) ± ribociclib (RIB). Annals of Oncology 2021;32:S1290-S1291.
28. Novartis. Data on file: NATALEE Clinical Study Report January 2023 Data Cut. 2023.
29. breastcancer.org. About Breast Cancer. Available from: https://www.breastcancer.org/about-breast-cancer. Accessed: 31 July 2023.
30. Łukasiewicz S, Czeczelewski M, Forma A, et al. Breast Cancer-Epidemiology, Risk Factors, Classification, Prognostic Markers, and Current Treatment Strategies-An Updated Review. Cancers (Basel) 2021;13:4287.
31. NHS. Symptoms: Breast cancer in women. 2019. Available from: https://www.nhs.uk/conditions/breast-cancer/symptoms/. Accessed: 18 April 2023.
32. NHS. Diagnosis: Breast cancer in women. 2019. Available from: https://www.nhs.uk/conditions/breast-cancer/diagnosis/. Accessed: 18 April 2023.
33. Cancer Research UK. Breast Screening. 2023. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/getting-diagnosed/screening-breast/. Accessed 22 October 2024.
34. Gómez HL, Castañeda CA, Vigil CE, et al. Prognostic effect of hormone receptor status in early HER2 positive breast cancer patients. Hematology/Oncology and Stem Cell Therapy 2010;3:109-115.
35. Rakha EA, Pinder SE, Bartlett JM, et al. Updated UK Recommendations for HER2 assessment in breast cancer. J Clin Pathol 2015;68:93-9.
36. Kay C M-PC, Meehan J, et al. Current trends in the treatment of HR+/HER2+ breast cancer. Future Oncol. 2021; 17(13):1665-1681.
37. Macmillan Cancer Support. Receptors for breast cancer. Available from: https://www.macmillan.org.uk/cancer-information-and-support/breast-cancer/receptors-for-breast-cancer. Accessed: 23 January 2023.
38. Hortobagyi GN, Connolly JL, D'Orsi CJ, et al. AJCC Cancer Staging Manual, Eighth Edition 2018.
39. National Cancer Institute. Early-stage breast cancer. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/early-stage-breast-cancer. Accessed: 18 April 2023.
40. American Cancer Society. Breast Cancer Stages. 2021. Available from: https://www.cancer.org/cancer/types/breast-cancer/understanding-a-breast-cancer-diagnosis/stages-of-breast-cancer.html. Accessed: 31 July 2023.
41. National Comprehensive Cancer Network (NCCN). Breast Cancer Guidelines, Version 4: Featured Updates to the NCCN Guidelines. Journal of the National Comprehensive Cancer Network 2023;21(6), 594-608.
42. Susini T, Biglia N, Bounous VE. Prognostic Factors Research in Breast Cancer Patients: New Paths. Cancers (Basel) 2022;14:971.

43. American Cancer Society. Breast Cancer Grade. 2021. Available from: https://www.cancer.org/cancer/types/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-grades.html. Accessed: 9 September 2024.
44. Rosen RD, Sapra A. TNM classification. StatPearls Publishing. 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK553187/. Accessed: 9 September 2024.
45. breastcancer.org. Screening and Testing: Oncotype DX Tests. 2023. Available from: https://www.breastcancer.org/screening-testing/oncotype-dx. Accessed: 25 October 2023.
46. breastcancer.org. Screening and Testing: Prosigna Breast Cancer Prognostic Gene Signature Assay. 2022. Available from: https://www.breastcancer.org/screening-testing/prosigna-assay. Accessed: 25 October 2023.
47. breastcancer.org. Screening and Testing: MammaPrint Test. 2023. Available from: https://www.breastcancer.org/screening-testing/mammaprint-test. Accessed: 25 October 2023.
48. breastcancer.org. Screening and Testing: EndoPredict Test. 2022. Available from: https://www.breastcancer.org/screening-testing/endopredict-test. Accessed: 25 October 2023.
49. Soliman NA, Yussif SM. Ki-67 as a prognostic marker according to breast cancer molecular subtype. Cancer Biol Med 2016;13:496-504.
50. Breast Cancer UK. About breast cancer: Facts and figures. Available from: https://www.breastcanceruk.org.uk/about-breast-cancer/facts-figures-and-qas/facts-and-figures/. Accessed: 18 April 2023.
51. Al-Ajmi K, Lophatananon A, Ollier W, et al. Risk of breast cancer in the UK biobank female cohort and its relationship to anthropometric and reproductive factors. PLoS One 2018;13(7):e0201097. 2018.
52. National Comprehensive Cancer Network (NCCN). Breast Cancer Guidelines, Version 5. 2024. Available from: https://www.nccn.org/login?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed: 22 October 2024. .
53. NICE. Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer. Diagnostics guidance [DG58]. Available from: https://www.nice.org.uk/guidance/dg58 [Accessed 26 September 2024].
54. Montemurro F, Aglietta M. Hormone receptor-positive early breast cancer: controversies in the use of adjuvant chemotherapy. Endocr Relat Cancer 2009;16:1091-102.
55. City of Hope. Breast cancer recurrence. 2023. Available from: https://www.cancercenter.com/cancer-types/breast-cancer/types/rare-breast-cancer-types/recurrent-breast-cancer. Accessed: 24 March 2023.
56. Anampa J, Makower D, Sparano JA. Progress in adjuvant chemotherapy for breast cancer: an overview. BMC Med 2015;13:195.
57. Park J, Rodriguez JL, O'Brien KM, et al. Health-related quality of life outcomes among breast cancer survivors. Cancer 2021;127:1114-1125.
58. John S, Broggio J. Cancer survival in England - adults diagnosed (2013-2017 edition). Office for National Statistics 2019. Available from:https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed. Accessed: 11 October 2024
59. Scharl A, Kühn T, Papathemelis T, et al. The Right Treatment for the Right Patient - Personalised Treatment of Breast Cancer. Geburtshilfe Frauenheilkd 2015;75:683-691.
60. Novartis. Shining a spotlight on the impact of breast cancer recurrence. 2024. Available from: https://www.novartis.com/uk-en/sites/novartis_uk/files/Shining%20a%20spotlight%20on%20the%20impact%20of%20breast%20cancer%20recurrence%20-%20April%202024.pdf Accessed: 3 September 2024.
61. Yussof I, Mohd Tahir NA, Hatah E, et al. Factors influencing five-year adherence to adjuvant endocrine therapy in breast cancer patients: A systematic review. Breast 2022;62:22-35.
62. McGuinness S, Hughes L, Moss-Morris R, et al. Adherence to adjuvant endocrine therapy among White British and ethnic minority breast cancer survivors in the United Kingdom. Eur J Cancer Care (Engl) 2022;31:e13722.
63. Chirgwin JH, Giobbie-Hurder A, Coates AS, et al. Treatment Adherence and Its Impact on Disease-Free Survival in the Breast International Group 1-98 Trial of Tamoxifen and Letrozole, Alone and in Sequence. J Clin Oncol 2016;34:2452-9.

64. Wulaningsih W, Garmo H, Ahlgren J, et al. Determinants of non-adherence to adjuvant endocrine treatment in women with breast cancer: the role of comorbidity. Breast Cancer Res Treat 2018;172:167-177.
65. Paranjpe R, John G, Trivedi M, et al. Identifying adherence barriers to oral endocrine therapy among breast cancer survivors. Breast Cancer Res Treat 2019;174:297-305.
66. Cusack L, Brennan M, Baber R, et al. Menopausal symptoms in breast cancer survivors: management update. Br J Gen Pract 2013;63:51-2.
67. Lambertini M, Arecco L, Woodard TL, et al. Advances in the Management of Menopausal Symptoms, Fertility Preservation, and Bone Health for Women With Breast Cancer on Endocrine Therapy. American Society of Clinical Oncology Educational Book 2023;43:e390442.
68. Marschner N, Zacharias S, Lordick F, et al. Association of Disease Progression With Health-Related Quality of Life Among Adults With Breast, Lung, Pancreatic, and Colorectal Cancer. JAMA Netw Open 2020;3:e200643.
69. Verrill M, Wardley AM, Retzler J, et al. Health-related quality of life and work productivity in UK patients with HER2-positive breast cancer: a cross-sectional study evaluating the relationships between disease and treatment stage. Health Qual Life Outcomes 2020;18:353.
70. Carreira H, Williams R, Funston G, et al. Associations between breast cancer survivorship and adverse mental health outcomes: A matched population-based cohort study in the United Kingdom. PLoS Med 2021;18:e1003504.
71. Burgess C, Cornelius V, Love S, et al. Depression and anxiety in women with early breast cancer: five year observational cohort study. Bmj 2005;330:702.
72. Obaidi JG, Al-Atiyyat NM. Quality of life among primary caregivers of women with breast cancer: A review. Middle East Journal of Cancer 2013;4:45-49.
73. Wagner CD, Bigatti SM, Storniolo AM. Quality of life of husbands of women with breast cancer. Psychooncology 2006;15:109-20.
74. University of Oxford. Cancer costs the UK economy £15.8bn a year. 2012. Available from: https://www.ox.ac.uk/news/2012-11-07-cancer-costs-uk-economy-%C2%A3158bn-year. Accessed: 1 April 2023.
75. Mohammadpour S, Soleimanpour S, Javan-Noughabi J, et al. A systemmatic literature review on indirect costs of women with breast cancer. Cost Eff Resour Alloc 2022;20:68.
76. Seweryn M, Banas T, Augustynska J, et al. The Direct and Indirect Costs of Breast Cancer in Poland: Estimates for 2017-2019. Int J Environ Res Public Health 2022;19.
77. Johnston SRD, Harbeck N, Hegg R, et al. Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE). J Clin Oncol 2020;38:3987-3998.
78. Toi M, Boyle F, Im Y-H, et al. Adjuvant Abemaciclib Combined with Endocrine Therapy: Efficacy Results in monarchE Cohort 1. The Oncologist 2023;28:e77-e81.
79. Novartis. Data on File: NATALEE Clinical Study Report April 2024 Data Cut. 2024.
80. Williams AD, Ruth K, Shaikh SS, et al. Should patients with hormone receptor-positive, HER2-negative breast cancer and one or two positive sentinel nodes undergo axillary dissection to determine candidacy for adjuvant abemaciclib? Cancer 2024;130:1052-1060.
81. Goel S, DeCristo MJ, McAllister SS, et al. CDK4/6 Inhibition in Cancer: Beyond Cell Cycle Arrest. Trends Cell Biol 2018;28:911-925.
82. Rader J, Russell MR, Hart LS, et al. Dual CDK4/CDK6 inhibition induces cell-cycle arrest and senescence in neuroblastoma. Clin Cancer Res 2013;19:6173-82.
83. Koboldt DC, Fulton RS, McLellan MD, et al. Comprehensive molecular portraits of human breast tumours. Nature 2012;490:61-70.
84. Kim S, Tiedt R, Loo A, et al. The potent and selective cyclin-dependent kinases 4 and 6 inhibitor ribociclib (LEE011) is a versatile combination partner in preclinical cancer models. Oncotarget 2018;9:35226-35240.
85. Chen P, Lee NV, Hu W, et al. Spectrum and Degree of CDK Drug Interactions Predicts Clinical Performance. Mol Cancer Ther 2016;15:2273-2281.
86. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. N Engl J Med 2016;375:1738-1748.
87. Hortobagyi GN, Stemmer SM, Burris HA, 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. Ann Oncol 2018;29:1541-1547.

88. Rugo HS, Harmer V, O'Shaughnessy J, et al. Quality of life with ribociclib versus abemaciclib as first-line treatment of HR+/HER2- advanced breast cancer: a matching-adjusted indirect comparison. Ther Adv Med Oncol 2023;15:17588359231152843.
89. ClinicalTrials.gov. A Trial to Evaluate Efficacy and Safety of Ribociclib With Endocrine Therapy as Adjuvant Treatment in Patients With HR+/HER2- Early Breast Cancer (NATALEE). 2018. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT03701334. Accessed: 20 August 2023.
90. Hudis CA, Barlow WE, Costantino JP, et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. J Clin Oncol 2007;25:2127-32.
91. Slamon DJ, Fasching PA, Hurvitz S, et al. Rationale and trial design of NATALEE: a Phase III trial of adjuvant ribociclib + endocrine therapy versus endocrine therapy alone in patients with HR+/HER2- early breast cancer. Ther Adv Med Oncol 2023;15:17588359231178125.
92. Novartis. Data on File: NATALEE Clinical Study Report Primary Pre-Planned Analysis of iDFS, July 2023 Data Cut. 2023.
93. Fasching PA, Stroyakovskiy D, Yardley D, et al. LBA13 Adjuvant Ribociclib Plus Nonsteroidal Aromatase Inhibitor in Patients With HR+/HER2− Early Breast Cancer: 4-Year Outcomes From the NATALEE Trial. Annals of Oncology 2024;35:S1207.
94. Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall Survival with Ribociclib plus Letrozole in Advanced Breast Cancer. New England Journal of Medicine 2022;386:942-950.
95. EORTC. EORTC QLQ-C30 Scoring Manual. 2001. Available from: https://www.eortc.org/app/uploads/sites/2/2018/02/SCmanual.pdf. Accessed: 11 October 2024.
96. EORTC. EORTC QLQ-BR23 Scoring Manual, 1996. Available from: https://www.eortc.be/qol/ScoringInstructions/BR23%20Summary.pdf. Accessed: 11 October 2024.
97. EuroQoL Research Foundation. EQ-5D-5L User Guide. Version 3. 2019. Available from: https://euroqol.org/wp-content/uploads/2023/11/EQ-5D-5LUserguide-23-07.pdf. Accessed: 11 October 2024.
98. Stern AF. The hospital anxiety and depression scale. Occup Med (Lond) 2014;64:393-4.
99. Hortobagyi GN. Ribociclib + Nonsteroidal Aromatase Inhibitor as Adjuvant Treatment in Patients With HR+/HER2- Early Breast Cancer: Final Invasive Disease-Free Survival Analysis From the NATALEE Trial [Oral presentation]. San Antonio Breast Cancer Symposium 2023.
100. He P LJ, Chen M, et al. Comparative efficacy and safety of extended adjuvant endocrine therapy for hormone receptor-positive early breast cancer: a Bayesian network meta-analysis. Breast Cancer Res Treat 2024;203:13-28.
101. Liao H, Pei W, Zhong J, et al. Efficacy and Safety of Initial 5 Years of Adjuvant Endocrine Therapy in Postmenopausal Hormone Receptor-Positive Breast Cancer: A Systematic Review and Network Meta-Analysis. Front Pharmacol 2022;13:886954.
102. Early Breast Cancer Trialists' Collaborative Group. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet 2015;386:1341-1352.
103. Bradley R, Braybrooke J, Gray R, et al. Aromatase inhibitors versus tamoxifen in premenopausal women with oestrogen receptor-positive early-stage breast cancer treated with ovarian suppression: a patient-level meta-analysis of 7030 women from four randomised trials. The Lancet Oncology 2022;23:382-392.
104. Ingle JN. Adjuvant endocrine therapy for postmenopausal women with early breast cancer. Clin Cancer Res 2006;12:1031s-1036s.
105. Phillippo DM, Ades AE, Dias S, et al. Methods for Population-Adjusted Indirect Comparisons in Health Technology Appraisal. Med Decis Making 2018;38:200-211.
106. Cheng D, Ayyagari R, Signorovitch J. The Statistical Performance of Matching-Adjusted Indirect Comparisons: Estimating Treatment Effects with Aggregate External Control Data. Ann Appl Stat 2020;14:1806-33., 2020.
107. Rastogi P, O'Shaughnessy J, Martin M, et al. Adjuvant Abemaciclib Plus Endocrine Therapy for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative, High-Risk Early Breast Cancer: Results From a Preplanned monarchE Overall Survival Interim Analysis, Including 5-Year Efficacy Outcomes. J Clin Oncol 2024;42:987-993.
108. Johnston SRD, Toi M, O'Shaughnessy J, et al. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer

(monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. Lancet Oncol 2023;24:77-90.
109. Phillippo DM, Ades AE, Dias S, et al. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submission to NICE. 2016. Available from: http://www.nicedsu.org.uk. Accessed: 23 October 2023.
110. Signorovitch JE, Sikirica V, Erder MH, et al. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. Value Health 2012;15:940-7.
111. ClinicalTrials.gov. Adj. Marker-adjusted Personalized Therapy Comparing ET+Ribociclib vs Chemotherapy in Intermediate Risk, HR+/HER2- EBC (ADAPTcycle). 2023. Available from: https://www.clinicaltrials.gov/study/NCT04055493?intr=ribociclib%20%2B%20ET&rank=4. Accessed: 22 September 2023.
112. Tripathy D, Im SA, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. Lancet Oncol 2018;19:904-915.
113. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Bmj 2021;372:n71.
114. Centre for Reviews and Dissemination University of York. Systematic reviews: CRD's guidance for undertaking reviews in health care. 2009. Available from: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf. Accessed: 29 August 2023.
115. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med 2017;377:122-131.
116. Martin M, Holmes FA, Ejlertsen B, et al. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2017;18:1688-1700.
117. Gnant M, Dueck AC, Frantal S, et al. Adjuvant Palbociclib for Early Breast Cancer: The PALLAS Trial Results (ABCSG-42/AFT-05/BIG-14-03). J Clin Oncol 2022;40:282-293.
118. Jongbloed EM, Blommestein HM, van Schoubroeck HM, et al. Cost-Effectiveness of Abemaciclib in Early Breast Cancer Patients: One Size Fits All or Tailoring to Patients' Needs? Breast Cancer (Dove Med Press) 2023;15:147-161.
119. Talwar A, Deshmukh A, Trivedi M, et al. Cost-effectiveness analysis of abemaciclib and endocrine therapy combination for the adjuvant treatment of HR+/HER2-, node-positive, high-risk, early breast cancer. Cancer Research 2023;83:4364-4364.
120. Chang S, Wang H, Wang Y, et al. EE183 Cost-Effectiveness Analysis of Early Versus Delayed Use of Abemaciclib Combination Treatment in Patients with HR+/HER2-High-Risk Early Breast Cancer: A US Payer Perspective. Value in Health 2022;25:S369.
121. Davie A, Molero, A., Goel, B. EE214: The Cost-Effectiveness of Abemaciclib Combined With Endocrine Therapy (ET) for the Treatment of Persons With HR+, HER2- Node Positive, Early Breast Cancer (EBC) at High Risk of Recurrence: A Spanish Healthcare Perspective. ISPOR Copenhagen. Value in Health 2023;26(11):S2.
122. Davie A, Traore S, Giovannitti M, et al. Cost-effectiveness analysis of abemaciclib with endocrine therapy (ET) versus ET alone for HR+, HER2-, node-positive, high-risk early breast cancer in Italy. Glob Reg Health Technol Assess 2023;10:62-69.
123. Zhong X, Chen P, He P, et al. Cost-Effectiveness Analysis of Adjuvant Endocrine Therapy With Ovarian Suppression in Premenopausal Patients With Hormone Receptor-Positive Early Breast Cancer in China. Clin Breast Cancer 2024;24:e41-e50.
124. Fariman S, Lafata J E. PT26 Health Economic Impact of Non-Persistence with Tamoxifen Adjuvant Endocrine Therapy in Pre-Menopausal Women with Early-Stage Breast Cancer: A Simulation Study. Value in Health 2024;27:S352.
125. Wei Q, Xu Y, Liu W, et al. Cost-effectiveness of abemaciclib plus endocrine therapy in high-risk HR+/HER2-early breast cancer in China. Cost Eff Resour Alloc 2023;21:91.
126. Sra MS, Sasi A, Batra A, et al. Cost-Effectiveness of Adjuvant Abemaciclib and Ribociclib in High-Risk Hormone Receptor-Positive Early Breast Cancer: An Indian Perspective. JCO Glob Oncol 2024;10:e2300433.
127. SMC. Abemaciclib 50mg, 100mg and 150mg film-coated tablets (Verzenios®). 2022. Available from: https://scottishmedicines.org.uk/medicines-advice/abemaciclib-verzenios-full-smc2494/. Accessed: 31 July 2023.
128. PBAC. ABEMACICLIB, Tablet 50 mg, Tablet 100 mg, Tablet 150 mg, Verzenio™, Eli Lilly Australia Pty Ltd. 2022. Available from:

https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2022-03/files/abemaciclib-psd-march-2022.pdf. Accessed: 25 October 2024.
129. CADTH. CADTH Reimbursement Review: Abemaciclib (Verzenio). 2022. Available from: https://www.cadth.ca/sites/default/files/DRR/2022/PC0282%20Verzenio%20-%20CADTH%20Final%20Recommendation%20(With%20Redactions)_Final.pdf. Accessed: 11 October 2024.
130. NCPE. Assessment Technical Summary Abemaciclib: Abemaciclib in combination with endocrine therapy for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence. 2023. Available from: https://www.ncpe.ie/wp-content/uploads/2023/08/Abemaciclib-22020-Technical-Summary.pdf. Accessed: 14 October 2024.
131. Fenix-Caballero S, Sanchez-Vegas A, Alegre Del-Rey EJ, et al. Economic assessment of abemaciclib for the adjuvant treatment of luminal HER2- breast cancer from the perspective of the Spanish health system. The European Journal of Health Economics 2024.
132. Galactionova K, Loibl S, Salari P, et al. Cost-effectiveness of palbociclib in early breast cancer patients with a high risk of relapse: Results from the PENELOPE-B trial. Front Oncol 2022;12:886831.
133. Slamon DJ, Neven P, Chia S, et al. Overall Survival with Ribociclib plus Fulvestrant in Advanced Breast Cancer (MONALEESA-3). N Engl J Med 2019;382:514-524.
134. Cuzick J, Sestak I, Baum M, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. The Lancet Oncology 2010;11:1135-1141.
135. European Medicines Agency. Abemaciclib Summary of Product Characteristics (SmPC). 2018. Available from: https://www.ema.europa.eu/en/documents/product-information/verzenios-epar-product-information_en.pdf. Accessed: 02 October 2024.
136. NICE. Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer [TA632]. 2020. Available from: https://www.nice.org.uk/guidance/ta632/history. Accessed: 1 November 2023.
137. Hamilton SN, Tyldesley S, Li D, et al. Second malignancies after adjuvant radiation therapy for early stage breast cancer: is there increased risk with addition of regional radiation to local radiation? Int J Radiat Oncol Biol Phys 2015;91:977-85.
138. Jackson C. Package 'flexsurv'. Flexible Parametric Survival and Multi-State Models. 2016. Available from: https://cran.r-project.org/web/packages/flexsurv/flexsurv.pdf. Accessed: 26 September 2016.
139. Latimer N. NICE DSU technical support document 14: survival analysis for economic evaluations alongside clinical trials-extrapolation with patient-level data. 2011. Available from: https://www.ncbi.nlm.nih.gov/books/NBK395885/pdf/Bookshelf_NBK395885.pdf. Accessed: 11 October 2024.
140. Janni W, Untch M, Harbeck N, et al. P1 02 01: Comparing the efficacy of aromatase inhibitors vs tamoxifen in hormone receptor positive, human epidermal growth factor receptor 2 negative early breast cancer: a systematic review and trial level meta analysis. San Antonio Breast Cancer Symposium December 6 10, 2022.
141. Rugo HS, O'Shaughnessy J, Boyle F, et al. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: safety and patient-reported outcomes from the monarchE study. Ann Oncol 2022;33:616-627.
142. Shao H, Zhao M, Guan A-J, et al. A network meta-analysis of efficacy and safety for first-line and second/further-line therapies in postmenopausal women with hormone receptor-positive, HER2-negative, advanced breast cancer. BMC Medicine 2024;22:13.
143. Lu Y-S, Mahidin EIBM, Azim H, et al. Final Results of RIGHT Choice: Ribociclib Plus Endocrine Therapy Versus Combination Chemotherapy in Premenopausal Women With Clinically Aggressive Hormone Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer. Journal of Clinical Oncology 2024;42:2812-2821.
144. Criscitiello C, Spurden D, Piercy J, et al. Health-Related Quality of Life Among Patients With HR+/HER2- Early Breast Cancer. Clin Ther 2021;43:1228-1244 e4.
145. Rider A, Bennett B, Williams R, et al. 160P The relationship between employment status, work productivity and activity impairment (WPAI) and health-related quality of life (HRQoL) for patients (pts) with HR+/HER2- early stage breast cancer (BC). Annals of Oncology 2021;32:S430.

146. PBAC. ABEMACICLIB, Tablet 50 mg, Tablet 100 mg, Tablet 150 mg, VerzenioTM, Eli Lilly Australia Pty Ltd. 2023. Available from: https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2023-03/files/abemaciclib-psd-03-2023.pdf. Accessed: 11 October 2024.
147. NICE. Fulvestrant for untreated locally advanced or metastatic oestrogen-receptor positive breast cancer [TA503]. 2018. Available from: https://www.nice.org.uk/guidance/ta503/history. Accessed: 01 November 2023.
148. NICE. TA612 Neratinib for extended adjuvant treatment of hormone receptor-positive, HER2-positive early stage breast cancer after adjuvant trastuzumab. 2019. Available from: https://www.nice.org.uk/guidance/ta612/evidence. Accessed: 16 October 2023.
149. Hudgens A FA, Tremblay G, Lloyd AJ, Phil D,. A Method of Deriving Estimates of Health State Utilities for Patients With Metastatic Breast Cancer. Journal of Clinical Pathways 2016;2:39-45.
150. NICE. Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma [TA306]. 2014. Available from: https://www.nice.org.uk/guidance/ta306/history. Accessed 01 November 2023.
151. NICE. Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy [TA579]. 2019. Available from: https://www.nice.org.uk/guidance/ta579. Accessed: 01 November 2023.
152. Nafees B, Stafford M, Gavriel S, et al. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes 2008;6:84.
153. Hernandez-Alava M WAaPS. Methods for mapping between the EQ 5D 5L and the 3L. NICE Decision Support Unit report. 2017. Available from: https://drive.google.com/file/d/1ehLw3-Mo7WyHFiwyijI4Ur5kCAPTEAPe/view. Accessed: 10 March 2022.
154. Hernández-Alava M PSaWA. Estimating the relationship between EQ-5D-5L and EQ-5D-3L: results from an English population study. Policy Research Unit in Economic Evaluation of Health and Care Interventions. Universities of Sheffield and York. Report 063. 2020. Available from: https://drive.google.com/file/d/1rkOWJqaX6NFCp0brYu1hWo-fndOmOXVx/view. Accessed: 10 March 2022.
155. NICE. Health Technology Evaluations: The Manual. Process and Methods [PMG36]. Economic Evaluation. 2022. Available from: https://www.nice.org.uk/process/pmg36/chapter/economic-evaluation. Accessed: 10 March 2022.
156. Cui J, Qian G. Selection of working correlation structure and best model in GEE analyses of longitudinal data. Communications in statistics—Simulation and computation® 2007;36:987-996.
157. pan-Canadian Oncology Drug Review. Final Economic Guidance Report - Ribociclib (Kisqali) for Metastatic Breast Cancer. 2018. Available from: https://www.cda-amc.ca/sites/default/files/pcodr/pcodr_pertuzumab-trastuzumab_perjeta-herceptin-combo_ebc_fn_egr.pdf. Accessed: 11 April 2019.
158. pan-Canadian Oncology Drug Review. Final Economic Guidance Report - Ribociclib (Kisqali) plus Fulvestrant for Advanced or Metastatic Breast Cancer. 2020. Available from: https://cadth.ca/sites/default/files/pcodr/Reviews2020/10195RibociclibFulvestrantMBC_fnEGR_NOREDACT-ABBREV_EC_22Apr2020_final.pdf. Accessed on: 20 August 2020.
159. Vitko AS, Martin P, Zhang S, et al. Costs of breast cancer recurrence after initial treatment for HR+, HER2-, high-risk early breast cancer: estimates from SEER-Medicare linked data. J Med Econ 2024;27:84-96.
160. Dell'Anno I, Ronconi G, Dondi L, et al. PT8 Five-Year Healthcare Resource Consumption and Direct Costs of Women with a New Diagnosis of Hr+/HER2- Breast Cancer Primary or Advanced: Analysis of a Large Italian Administrative Database. Value in Health 2023;26:S254.
161. Earla JR, Kurian AW, Kponee-Shovein K, et al. EE458 Economic Burden of Disease Recurrence in Elderly Patients With Human Epidermal Growth Factor Receptor 2-Negative (HER2–) Early Breast Cancer (eBC). Value in Health 2024;27:S141.
162. Wu VS, Khlopin M, Chadha M, et al. Out-of-Pocket Cost Modeling of Adjuvant Antiestrogen and Radiation Therapy After Lumpectomy for Early-Stage Breast Cancer Across Medicaid and Medicare Plans. Int J Radiat Oncol Biol Phys 2024;119:1379-1385.
163. Lao C, Mondal M, Kuper-Hommel M, et al. Differences in Breast Cancer Costs by Cancer Stage and Biomarker Subtype in New Zealand. Pharmacoecon Open 2022;6:539-548.

164. Valsecchi D, Buzzatti G, Caputo R, et al. Epidemiology and choice of treatment in the adjuvant setting of hormone receptor positive HER2 negative (HR+/HER2-) breast cancer (BC), evidence from administrative databases, with a focus on the SARSCOV2 pandemic. Tumori Journal 2022;108:60.
165. Berdunov V, Millen S, Paramore A, et al. 61P Estimating the cost of adjuvant chemotherapy in ER+/HER2- early breast cancer and distant recurrence of breast cancer in the UK. Annals of Oncology 2021;32:S46.
166. Brezden-Masley C, Fathers KE, Coombes ME, et al. A population-based comparison of treatment patterns, resource utilization, and costs by cancer stage for Ontario patients with hormone receptor-positive/HER2-negative breast cancer. Breast Cancer Res Treat 2021;185:507-515.
167. Brandao M, Morais S, Lopes-Conceicao L, et al. Healthcare use and costs in early breast cancer: a patient-level data analysis according to stage and breast cancer subtype. ESMO Open 2020;5:e000984.
168. Calip GS, Cueto J, Hoskins KF, et al. Patient-reported healthcare utilization among Medicare beneficiaries with HR-positive, HER2-negative early breast cancer. European Journal of Cancer 2020;138:S108-S109.
169. Vaz-Luis I, Hughes ME, Cronin AM, et al. Variation in type of adjuvant chemotherapy received among patients with stage I breast cancer: A multi-institutional study. Cancer 2015;121:1937-48.
170. Zheng D, Thomas Jr. Adherence to and persistence with adjuvant hormone therapy, healthcare utilization, and healthcare costs among older women with breast cancer: A population-based longitudinal cohort study. J Geriatr Oncol 2023;14:101599.
171. Perrone V, Giacomini E, Sangiorgi D, et al. Description of characteristics, management of care and healthcare direct costs of patients with HR+/HER2- early breast cancer in Italy: a real-world study involving administrative and pathological anatomy databases. Expert Rev Pharmacoecon Outcomes Res 2023;23:1077-1085.
172. Berdunov V, Cuyun Carter, G., Laws, E., Luo, R., Russell, C., Campbell, S., Abdou, Y., & Force. HSR22-129: The Cost of Treatment of HR+/HER2- Early Breast Cancer and Implications for the Cost-Effectiveness of Multigene Assays in the US. Journal of the National Comprehensive Cancer Network 2020; 20(3.5): HSR22-129-HSR22-129.
173. Goetz MP, Cicin I, Testa L, et al. Impact of dose reductions on adjuvant abemaciclib efficacy for patients with high-risk early breast cancer: analyses from the monarchE study. npj Breast Cancer 2024;10:34.
174. NHS. National Cancer Drugs Fund list. Version 1.329. 2024. Available from: https://www.england.nhs.uk/wp-content/uploads/2017/04/national-cdf-list-v1.329.pdf. Accessed: 21 October 2024.
175. Turner NC, Ro J, André F, et al. Palbociclib in Hormone-Receptor–Positive Advanced Breast Cancer New England Journal of Medicine 2015;373:209-219.
176. Sledge Jr GW, Toi M, Neven P, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2− advanced breast cancer who had progressed while receiving endocrine therapy. J Clin Oncol 2017;35:2875-2884.
177. Piccart M, Hortobagyi GN, Campone M, et al. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2. Ann Oncol 2014;25:2357-2362.
178. Finn RS, Crown JP, Ettl J, et al. Efficacy and safety of palbociclib in combination with letrozole as first-line treatment of ER-positive, HER2-negative, advanced breast cancer: expanded analyses of subgroups from the randomized pivotal trial PALOMA-1/TRIO-18. Breast Cancer Res 2016;18:67.
179. Goetz MP, Toi M, Campone M, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. J Clin Oncol 2017;35:3638-3646.
180. Chia S, Gradishar W, Mauriac L, et al. Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFECT. J Clin Oncol 2008;26:1664-70.
181. Bachelot T, Bourgier C, Cropet C, et al. Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor–positive, human epidermal growth factor receptor 2–negative metastatic breast cancer with prior exposure to aromatase inhibitors: A GINECO study. J Clin Oncol 2012;30:2718-2724.

182. Genentech Inc. XELODA [package insert]. 2022. Available from: https://www.gene.com/download/pdf/xeloda_prescribing.pdf. Accessed: 16 October 2023.
183. European Medicines Agency. Capecitabine Summary of Product Characteristics (SmPC). 2023. Available from: https://www.ema.europa.eu/en/documents/product-information/xeloda-epar-product-information_en.pdf. Accessed: 01 November 2023.
184. European Medicines Agency. Alpelisib Summary of Product Characteristics (SmPC). 2020. Available from: https://www.ema.europa.eu/en/documents/product-information/piqray-epar-product-information_en.pdf Accessed: 29 September 2024.
185. European Medicines Agency. Paclitaxel Summary of Product Characteristics (SmPC). 2009. Available from: https://www.ema.europa.eu/en/documents/product-information/abraxane-epar-product-information_en.pdf Accessed: 03 October 2024.
186. NHS. NHS Reference Costs 2022/2023. 2024. Available from: https://app.powerbi.com/view?r=eyJrIjoiOTQwZjIwMjUtNDgwMi00MThmLWJhM2MtNmM5YWY2MTkwM2M4IiwidCI6IjM3YzM1NGIyLTg1YjAtNDdmNS1iMjIyLTA3YjQ4ZDc3NGVlMyJ9. Accessed: 03 October 2024.
187. Simcock R, Heaford A. Costs of multidisciplinary teams in cancer are small in relation to benefits. Bmj 2012;344:e3700.
188. NICE. Advanced breast cancer: diagnosis and treatment [CG81]. 2009. Available from: https://www.nice.org.uk/guidance/cg81. Accessed: 01 November 2023.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ribociclib with an aromatase inhibitor for the adjuvant treatment of hormone receptor-positive, HER2-negative early breast cancer [ID6153]

Summary of Information for Patients (SIP)

30th October 2024

File name	Version	Contains confidential information	Date
ID6153_Ribociclib_NICE_SIP [NoCON]	Final	No	30th October 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. 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 for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** 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 name: Ribociclib

Brand name: Kisqali®

1b) Population this treatment will be used by: Please outline the main patient population that is being appraised by NICE:

The main patient population addressed in this submission is adults with hormone receptor positive (**HR-positive**), human epidermal growth factor receptor 2 negative (**HER2-negative**) **early breast cancer** that is at high **risk of recurrence** following surgery of the **primary breast tumour**. These terms are explained below:

Breast cancer tumour cells may have **receptors** (**proteins**) that **hormones** or proteins can attach to and encourage the cells to grow. Breast cancer tumours that have receptors for the hormones oestrogen or progesterone are called HR-positive breast cancers. Some breast cancer tumours have receptors called human epidermal growth factor receptor 2 (**HER2**) on the surface of their cells. Breast cancer tumours without this receptor are called HER2-negative breast cancers.

Early breast cancer means that the cancer is only present in the breast tissue and surrounding **lymph nodes** and has not spread to other parts of the body. The term 'at high risk of recurrence' means that there is a chance that the breast cancer may come back after initial treatment has been completed.

Finally, the term primary breast tumour refers to the tumour where the cancer first started growing. Patients with early breast cancer usually have surgery to remove the primary tumour (see **Section 2c**). Ribociclib would be prescribed to patients with early breast cancer following surgery of the primary breast tumour.

This submission considers four populations of patients. The first is the main patient population described above i.e. patients with HR-positive, HER2-negative early breast that is at high risk of recurrence. This is referred to as **Population 1**.

Within Population 1, there are three subgroups of patients which are also considered in this

submission:

1) Patients with *node-positive* disease (i.e. the cancer has spread to lymph nodes). This population is referred to as **Population 2**
2) Patients with *node-negative* disease (i.e. the cancer has not spread to any lymph nodes). This population is referred to as **Population 3**
3) Patients who, based on specific features of their breast cancer, are suitable for a treatment called abemaciclib (see **Section 2c**). This population is referred to as **Population 4**.

Please note: Further explanations for the words and phrases highlighted in **blue bold text** are provided in the glossary (**Section 4b**). Cross-references to other sections or documents are highlighted in **orange**.

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.

A **marketing authorisation** (licence) extension application for ribociclib as a treatment for patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence is currently pending from the **European Medicines Agency** (EMA). The anticipated date of EMA approval is confidential. More information can be found in **Document B** in **Section B.1.2**.

At high risk of recurrence is defined as per the inclusion criteria of the NATALEE clinical trial (the pivotal trial for ribociclib in this indication),as adults with HR-positive, HER2-negative EBC and:

- Anatomical Stage IIA
  - N0 with either:
    - Grade 2 with any of the following criteria:
      - Ki67 ≥20%,
      - Oncotype DX, Breast Recurrence Score ≥26,
      - Prosigna/PAM50 categorised as high risk,
      - MammaPrint categorised as high risk or EndoPredict EPclin Risk Score categorised as high risk
    - Grade 3
  - N1
- Anatomical Stage IIB
  - N0 or N1
- Anatomical Stage III
  - N0, N1, N2 or N3

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:

Funding was provided to Breast Cancer Now for projects directed on making positive impact on the breast cancer care and healthcare system, as well as patient support provision:

- *Breast Cancer Now Service Pledge 2023-2024 (sponsorship).* The project is focused on service improvements and lasts for two years. Within the pledge Breast Cancer Now provides support and guidance throughout the process and actively involves people with different perspectives of breast cancer, to develop a more complete understanding of the challenges and opportunities to improve treatment and care. The project was jointly supported by Novartis along with other pharma companies.
    - Funding amount: £109,985 (across two years)
- *Breast Cancer Now Nursing Conference 2024 (sponsorship).* The conference is a platform for expert speakers to talk on specialist areas such breast cancer and menopausal symptoms, lobular breast cancer and breast reconstruction. It is a moment for nurses to come together to expand their network, knowledge and CPD professional development.
    - Funding amount: £15,000

Funding was provided to Make2ndsCount for projects directed on making positive impact on the breast cancer care and healthcare system, as well as patient support provision in metastatic breast cancer:

- *Secondary Breast Cancer Patient Summit (sponsorship).* The summit is platform that educates and updates women and men on the management and treatment of secondary breast cancer and enables patients to meet and make connections with fellow patients and members of the clinical community.
    - Funding amount: £10,000

Funding was provided to Maggie's for projects directed on making positive impact on the breast cancer care and healthcare system, as well as patient support:

- *Getting Started* (grant) program. Maggie's courses are aimed at helping patients understand what's involved with treatment and breast cancer care and meeting others in similar situations.
    - Funding amount: £60,000

Funding was provided to Let's talk about...Black women and breast cancer for a project directed on raising awareness or breast cancer and inequalities of care:

- *'Let's talk about…Black women and breast cancer'* health awareness day (sponsorship). The day specifically targets education of black women to help improve knowledge and understanding of breast health in general in the community. It is a one-day educational seminar covering a broad range of areas ranging from health prevention through to diagnosis and treatment.
    - Funding amount: £8,000

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.

Ribociclib is anticipated to treat patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence (including patients with node-positive or node-negative disease, and patients who are suitable for treatment with abemaciclib)

What is HR-positive, HER2-negative early breast cancer?

Breast cancer is a cancer that starts within the breast tissue; it mainly affects women, although it can also occur in men. Breast cancer develops when abnormal cells within the breast multiply uncontrollably, forming a lump of abnormal cells called a tumour.

Breast cancer cells may have receptors (proteins) that hormones or proteins can attach to and encourage the cells to grow. Hormones are small chemical substances that carry messages via the bloodstream to coordinate different functions of the body. In HR-positive breast cancer, the binding of hormones such as oestrogen and/or progesterone to receptors on the surface of breast tumour cells stimulates cancer cells to divide, causing the tumour to grow as a result.[1] Cancerous cells from the tumour may then invade nearby tissues and spread to other parts of the body. Breast cancer cells may also have the protein HER2 on the surface. Breast cancers without the HER2 proteins are considered to be HER2-negative. The most common subtype of breast cancer is HR-positive, HER2-negative breast cancer, accounting for 68% of all breast cancers.[2]

Breast cancers can also be classified based on how far the breast cancer tumour has spread within the body, including whether the cancer is present in in lymph nodes (**nodal status**). Early breast cancer is early **stage** breast cancer (see Section 2b) where cancerous cells are not found beyond the breast and nearby lymph nodes. Lymph nodes are small structures that form part of the **immune system;** their role is to help prevent infections by trapping germs and abnormal cells. People have multiple lymph nodes across different parts of the body, including the underarms, neck, and groin. If a breast cancer spreads to lymph nodes that are far from the breast and/or to other organs of the body, it is considered to be **advanced** or **metastatic breast cancer**, rather than early breast cancer. The term early breast cancer is described in more detail in Section 2b below.

Additionally, following the completion of treatment for early breast cancer (Section 2c), there is a risk that the cancer could come back. Certain disease characteristics influence the risk of the cancer coming back, such as the type of breast cancer (for example, what receptors are present), the stage (i.e. the tumour size, nodal status, and spread; see Section 2b), the **grade,** and different genetic factors. Cancer that comes back is termed recurrent cancer. Breast cancer recurrence can happen months or years after initial treatment ends. At 20 years, the risk of breast cancer recurring (coming back) among patients with HR-positive, HER2-negative ranges from 10–41% (meaning that the breast cancer comes back for approximately 1 to 4 in every 10 patients),[3] and over half of recurrences occur more than 5 years after diagnosis.[4] Unfortunately, recurrent breast cancer is more likely to progress to advanced or metastatic breast cancer which has low survival rates.

The main patient population of interest in this submission is patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence. High risk of recurrence is determined based on the characteristics mentioned above, including tumour stage, grade and genetic factors. Three subgroups of patients within this broad population are also addressed: patients with node-positive disease, patients with node-negative disease, and patients who are eligible to be treated with abemaciclib (see Section 1a).

What are the signs and symptoms of breast cancer?

Breast cancer typically presents as a lump or area of thickened breast tissue. Other common symptoms of breast cancer include nipple discharge (fluid from the nipple), breast or nipple pain, rashes around or on the nipple, nipple retraction (when the nipple turns inwards), swollen

lymph nodes in the armpit or near the collar bone, or skin dimpling on the breast.

What causes breast cancer?

It is not fully understood what causes breast cancer. However, there are some known risk factors that may affect someone's chance of developing breast cancer. Some risk factors are associated with lifestyle (e.g. lack of physical activity, obesity, high alcohol intake, smoking, and excessive exposure to ultraviolet light), while other risk factors are unchangeable (e.g. sex, age, family history, and reproductive history).[5]

How does breast cancer progress over time?

Over time, the cancerous cells in a tumour can continue to divide uncontrollably, causing the tumour to grow rapidly. Cells from the tumour may spread to lymph nodes close to the breast, and may also spread further to more distant lymph nodes and organs. Common sites for breast cancer cells to spread to include the bones, liver, brain or lungs. Once cancer has spread to other parts of the body, the cancer is called advanced or metastatic breast cancer. Advanced or metastatic breast cancer can no longer be cured and is associated with considerably lower chances of survival.

How many people get breast cancer?

Breast cancer is the most common cancer in the United Kingdom (UK), with approximately 56,800 new cases diagnosed every year.[6] Most breast cancers are diagnosed as early breast cancer (before the breast cancer has spread to distant lymph nodes and/or to other organs of the body).[7] Only 5% of breast cancer patients (5 in every 100 breast cancer patients) in England are diagnosed with advanced or metastatic breast cancer.[7] Regrettably, in the UK, breast cancer is the fourth most common cause of cancer death, and the second most common in women, accounting for approximately 11,500 deaths in women and 85 deaths in men each year.[6]

What is the impact of breast cancer (disease burden)?

Living with breast cancer can be difficult for both patients and those who look after them (caregivers).

Patients with breast cancer are impacted by their disease symptoms, treatment **side effects** and anxieties surrounding their disease. These factors frequently negatively impact patients' overall **quality of life** (a measure of overall enjoyment of life), particularly if the breast cancer recurs (comes back) and/or progresses (gets worse and/or spreads to other parts of the body).[8]

For example, some current breast cancer treatments can cause unpleasant side effects which negatively impact patients' day-to-day lives. The main treatments for early breast cancer include **hormone therapy** and **targeted treatments**. These treatments are described in more detail in Section 2c. Patients receiving hormone therapy treatments may experience side effects such as **fatigue** (feeling tired), **nausea** (feeling sick), and changes in appetite,[9] while patients receiving targeted treatments may experience other side effects such as diarrhoea.[10]

Additionally, following the completion of treatment for early breast cancer, there remains a risk that the cancer could come back (recurrent cancer). As recurrent breast cancer is more likely to progress to advanced or metastatic breast cancer, which is incurable, the fear of breast cancer recurrence is common among patients with breast cancer and among patients who are recovering from breast cancer. In recent surveys, 81% of breast cancer patients reported that

they have experienced fear of recurrence.[11] Fear of recurrence has been shown to have a large impact on patients' mental wellbeing, with one in five respondents agreeing that fear of recurrence impacts their relationships, leisure time, and travel plans.[11]

What are the personal, financial and societal costs of breast cancer?

The identification and treatment of breast cancer costs the National Health Service (NHS) an estimated £1.5 billion every year (based on data from 2012).[12] This includes both direct costs of breast cancer, for example using healthcare resources (e.g. treatment costs, clinical tests and procedures, and medical visits), and indirect costs, for example through patients and caregivers being less able, or unable to continue working.[13, 14]

Patients with breast cancer may have to take time off work to receive treatment in hospital or if breast cancer symptoms, or treatment side effects, make them feel too unwell. A survey conducted among working-age breast cancer patients in 2019 reported that approximately 4 in every 10 patients stopped working after receiving a breast cancer diagnosis.[15] Among patients who remained at work, patients reported themselves to be less productive post-diagnosis compared with pre-diagnosis. Likewise the study found that 15 in every 100 employed caregivers leave their jobs after starting to care for a patient with breast cancer.[15]

The introduction of more effective and well-**tolerated** treatments for breast cancer would benefit not only patients and their caregivers, but also reduce the substantial financial burden of breast cancer on the NHS and UK economy.

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?

How is breast cancer diagnosed?

The UK has a **breast cancer screening** programme which invites all females aged 50–70 for breast cancer screening every 3 years. This involves screening healthy women using a **mammogram** (a low-dose x-ray of the breast). The goal of the breast cancer screening programme is to detect breast cancer at an early stage when it has the best chance of being treated successfully.[16] Outside of routine breast cancer screening, people with symptoms of breast cancer (Section 2a) are referred to breast clinics to undergo specialist testing. Tests used to diagnose breast cancer might include mammograms, breast **ultrasounds** (a test that uses high frequency sound waves to create a picture of the inside of the breast) and **biopsies** (taking a small sample of the breast tissue and analysing it with a microscope to determine if the cells are cancerous, and if so, the specific type of breast cancer present).[17]

Breast cancer staging

If a diagnosis of breast cancer is confirmed, the doctor will investigate how much the breast cancer has grown (tumour size) and whether it has spread from where it started in order determine its 'stage'. Determining the stage of breast cancer can help understand how the disease will likely progress and respond to treatment. A description of each breast cancer stage is provided in **Table 1**.

Stage 1, 2 or 3 breast cancers are considered to be early breast cancers (i.e. the cancer has not spread to tissues or organs away from the breast). Stage 4 breast cancer is considered advanced or metastatic breast cancer (i.e. the cancer has spread to other parts of the body

beyond its original location) [**Table 1**].[18]

Table 1: Stages of breast cancer

Stage	Description
1	• The tumour is 2cm or smaller • No (or a tiny number of) cancer cells are found in lymph nodes in the armpit • The cancer may not be found in the breast but cancer cells have spread to lymph nodes in the armpit
2	• The tumour is up to or bigger than 5cm • The cancer may or may not have spread to the lymph nodes under the arm • The cancer may not be found in the breast but cancer cells have spread to 1 to 3 lymph nodes in the armpit or near the breast bone
3	• The cancer has spread to lymph nodes in the armpit and sometimes to other lymph nodes nearby • It may have spread to the skin of the breast or to the chest muscle • Sometimes the cancer cannot be found in the breast or is small but has spread to 4 to 9 lymph nodes in the armpit
4	• Cancer has spread to tissues or organs away from the breast. Common sites for breast cancer to spread to are the brain, bones, liver and lungs • Stage 4 breast cancer is also called advanced or metastatic cancer

Footnotes: Stage 1–3 breast cancer is considered early breast cancer; Stage 4 breast cancer is considered advanced or metastatic breast cancer.
Source: Macmillan Cancer Support.[19]

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.

What are the current treatment options for breast cancer?

Different factors determine which treatment options are most suitable for patients with newly diagnosed early breast cancer. These factors include the stage of disease (Section 2b), the sensitivity of the tumour to hormones (Section 2a), whether the patient has experienced the menopause or not, and the risk of the breast cancer recurring (coming back) following initial surgery of the primary breast tumour.

In the UK, it is recommended that patients with early breast cancer undergo surgery to remove the primary breast tumour, whilst also receiving treatment.[20] Patients may undergo treatment *before* surgery (known as **neoadjuvant** therapy) and/or undergo treatment *after* surgery

(known as **adjuvant** therapy).

The figure on the next page illustrates the current treatment pathway available to patients with early breast cancer in the UK, and highlights where ribociclib, the new treatment being proposed in this submission, would fit within the treatment pathway (

Figure 1).

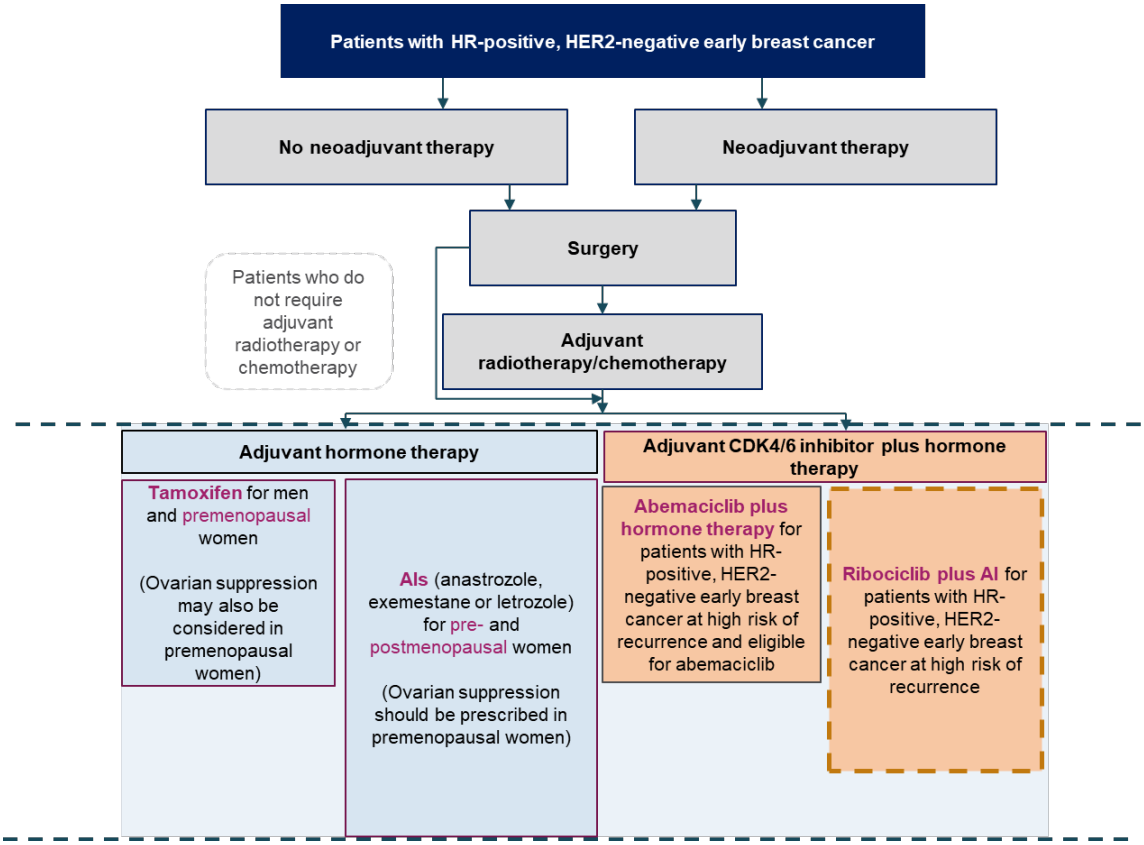
Neoadjuvant therapy

Before undergoing surgery, patients may be offered **chemotherapy** to shrink the tumour size before removal during surgery. Alternatively, women have experience the menopause who do not require chemotherapy may instead be offered hormone therapy prior to surgery.[20]

What is hormone therapy?

HR-positive cancer cells are stimulated to grow and divide when hormones, such as oestrogen and progesterone, bind to them. Hormone therapy stops or slows down the growth of HR-positive tumours by either reducing the amount of hormone that is made by the body, or by making the cancer cells less sensitive to the hormone. As a result, the cancer cells do not receive signals from hormones to divide, so tumour growth slows down or stops.[1]

Figure 1: Current treatment pathway for HR-positive, HER2-negative early breast cancer in the UK, and the proposed positioning of ribociclib



Abbreviations: AI: aromatase inhibitor; CDK4/6: cyclin dependent kinase 4 and 6; HER2: human epidermal growth factor receptor 2; HR: hormone receptor.
Source: Adapted from NICE Guideline NG101.[20]

Adjuvant therapy

After receiving surgery to remove part or all of the primary breast tumour, patients may be

offered treatment to kill or slow down the growth of any remaining cancer cells. This is called adjuvant therapy. Patients may be offered chemotherapy after surgery, or an alternative treatment option is **radiotherapy** across all or part of the breast.[20]

Beyond chemotherapy and radiotherapy, the most common type of adjuvant therapy for patients with HR-positive breast cancer tumours is hormone therapy. Men, premenopausal women, and postmenopausal women with early breast cancer that is at low risk of recurrence (coming back) may be offered a treatment called tamoxifen, which blocks the hormone receptor protein on cancer cells. This means hormones can no longer bind to the receptors, so the growth of the tumour is slowed down. Postmenopausal women with early breast cancer deemed to be at high risk of returning are offered a different class of hormone therapy called an **aromatase inhibitor (AI)**, which reduces the amount of oestrogen produced meaning there is less oestrogen present to stimulate tumour growth.[20]

More recently, a different, new treatment has been made available for patients with early breast cancer called abemaciclib. Abemaciclib is a type of targeted treatment that can be given to patients receiving hormone therapy specifically if their breast cancer has spread to nearby lymph nodes and if there is a high risk of the cancer returning. Abemaciclib blocks the division of rapidly dividing breast cancer cells, by blocking the action of two proteins called cyclin-dependent kinases 4 and 6 (**CDK4** and **CDK6**) which are involved in encouraging cells to divide. As a result, abemaciclib stops or slows down the growth of breast cancer tumours. However, as patient suitability for treatment with abemaciclib depends on several factors, such as having node-positive disease, only approximately 14% of patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence meet the criteria required to be treated with abemaciclib.[21]

It is anticipated that ribociclib will represent a new treatment option for patients with HR-positive, HER2-negative early breast cancer at high risk of breast cancer recurrence following surgery. Ribociclib is to be taken in combination with AI therapy and like abemaciclib, ribociclib is a blocker of CDK4 and CDK6. However, compared to abemaciclib, ribociclib is anticipated to be suitable for a broader population of patients with early breast cancer. This is because ribociclib is anticipated to be suitable for patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence, regardless of whether their cancer has spread to nearby lymph nodes. In contrast, abemaciclib is only recommended in patients whose cancer has spread to nearby lymph nodes and has extra high-risk features. As a result, it is anticipated that ribociclib will provide a new treatment option for a broader population of patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence.

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.

Breast cancer from the patient perspective

Living with breast cancer can be both mentally and physically challenging. Patients with early breast cancer report a reduction in their quality of life after diagnosis, which gets even worse if the cancer becomes more advanced or returns. Factors that contribute to reducing patients' quality of life include the symptoms of their cancer, side effects caused by treatment, effects on mental health, and reductions in patients' ability to work and carry out daily tasks.[22, 23] As described in **Section 2a**, the fear of the breast cancer returning is a major source of anxiety, with 81% of patients with breast cancer reporting that they have experienced fear of cancer recurrence.

Approximately 1 to 4 in every 10 patients with early breast cancer who receive hormone therapy are at risk of the cancer returning.[3] Breast cancer that returns often comes back as advanced or metastatic cancer, meaning it is incurable and associated with a lower likelihood of survival.[24]

The effects of breast cancer can also reduce the quality of life of caregivers and family members. Caregivers often face physical, emotional, social and financial challenges whilst caring for patients with breast cancer, all of which can compromise caregivers' quality of life.[25] For example, family members of patients with breast cancer have been reported to have poorer quality of life than family members of healthy women.[26]

As discussed in **Section 2a**, the ability of both patients and their caregivers to work is often reduced following a diagnosis of breast cancer. Loss or reduction of income can add financial stress to patients and their families coming to terms with a breast cancer diagnosis. Furthermore, stopping work can worsen the sense of social isolation experienced by breast cancer patients.

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.

What is ribociclib?

The new treatment being assessed in this submission is called ribociclib. Ribociclib is a type of targeted cancer treatment that blocks cancer growth. Ribociclib targets two proteins, called CDK4 and CDK6, which play a role in stimulating cancer cells to divide and grow.[27]

As such, by blocking the action of CDK4 and CDK6, ribociclib prevents or slows the growth and spread of breast cancer tumours.

Ribociclib, in combination with hormone therapy, is already available as a treatment for women with HR-positive, HER2-negative locally advanced or advanced breast cancer.[28]

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes

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.

What other medicines must be taken at the same time as ribociclib?

Ribociclib is intended to be used in combination with either letrozole, anastrozole, or exemestane. Letrozole, anastrozole, and exemestane are AI therapies (a type of hormone therapy medicine). Men and premenopausal women should also take goserelin (a different hormone therapy) in combination with ribociclib and AI therapy.

AI therapy, such as letrozole, anastrozole, and exemestane, blocks the production of oestrogen which, as described in **Section 2a**, plays an important role in the growth of HR-positive breast cancers. By blocking the production of oestrogen, AI therapy reduces the amount of oestrogen circulating the body. This means cancer cells receive fewer signals to stimulate growth.

Ribociclib and AI therapy both prevent the multiplication of cancer cells but do so in different ways. As outlined in **Section 3a**, ribociclib inhibits the activity of CDK4 and CDK6 proteins involved in cell division, while AI therapy prevents the production of oestrogen.

Details of the administration and dosing of ribociclib as well as the administration and dosing of the hormone therapy medicines that patients must take at the same time as ribociclib are provided in **Section 3c.**

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?

How is ribociclib taken?

Ribociclib is available as a tablet, and should be taken orally (by mouth). Patients can take ribociclib at home. They are not required to travel to hospital or other health care settings to receive ribociclib.

Patients should take a total of 400 mg of ribociclib (2 x 200 mg tablets) once daily for 21 consecutive days, followed by 7 days not taking ribociclib. This results in a complete **treatment cycle** of 28 days.

What other medicines must be taken at the same time as ribociclib?

Ribociclib should be taken together with a hormone therapy medicine, specifically AI therapy. This AI therapy is typically either letrozole, anastrozole, or exemestane. These medicines are in tablet form and should be taken orally. Patients should take 2.5 mg letrozole (one tablet), 1 mg anastrozole (one tablet) or 25 mg exemestane (one tablet) once daily on every day of the 28-day treatment cycle.

For premenopausal women and men, an additional therapy called goserelin should be taken. These patients should receive 3.6 mg goserelin once every 28 days. Goserelin is given as a small pellet which is injected under the skin. The pellet releases the drug slowly as it dissolves. Patients must attend hospital to receive goserelin.

How long should ribociclib be taken for?

Treatment with ribociclib in combination with AI therapy should be continued for 3 years. However, treatment with ribociclib may be stopped sooner if any side effects are too severe or if the breast cancer recurs (comes back).[28]

What is a treatment cycle?

Many cancer treatments are given in treatment cycles. Typically each treatment cycle is split into a time period where patients receive treatment (called 'on-treatment'), followed by a time period where patients do not receive treatment (called 'off-treatment'). The off-treatment period is to allow the body to recover. The length of a treatment cycle and the split between the on-treatment and off-treatment periods can vary depending on the type of treatment being given. For patients taking ribociclib, one complete treatment cycle lasts 28 days before the next treatment cycle begins.

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.

Studies of ribociclib in early breast cancer

There has been one key **clinical trial** which has studied how well ribociclib works in patients with HR-positive, HER2-negative early breast cancer that is at high risk of recurrence. The clinical trial is called **NATALEE** and is described in more detail below.

NATALEE is an ongoing, global, **Phase 3**, multicentre clinical trial.[29] This means that the clinical trial is still running, and it is being conducted across the world, at a number of clinical trial sites. Phase 3 clinical trials typically compare the **effectiveness** (how well a treatment works) and safety (side effects) of a new treatment against current existing treatment(s).

Patients with early breast cancer were able to participate in NATALEE if they met the following criteria:[29]

- Men and women with HR-positive, HER2-negative breast cancer at high risk of recurrence (Section 2a)
- Patients with Stage 2 or 3 breast cancer (Section 2b)
- If patients had received radiotherapy, the radiotherapy had to have been completed before or after surgery
- If patients had received chemotherapy, the chemotherapy had to have been completed before or after surgery
- Patients were eligible to receive adjuvant hormone therapy for 60 months

Patients in NATALEE were randomly allocated to one of the following treatment groups:

- Ribociclib (for 36 months) plus AI therapy (for 60 months)
- AI therapy (for 60 months)

In NATALEE, the effectiveness of ribociclib plus AI therapy (compared to AI therapy alone) was measured by assessing the risk of developing recurrent disease while receiving treatment.

The main outcome assessed in NATALEE was invasive disease-free survival. This outcome assesses the number of patients in each treatment group who are alive and free of any **invasive breast cancer** (cancer that has spread into surrounding breast tissue) or any other type of cancer.

Other effectiveness outcomes in NATALEE included recurrence-free survival (assessing any disease recurrence), distant disease-free survival (assessing any disease recurrence in areas away from the breast), and overall survival (assessing whether patients have died).[29]

Results for these outcomes from NATALEE are presented in **Section 3e.**

More information about NATALEE can be found here:

- ClinicalTrials.gov (NATALEE) (Study Details | A Trial to Evaluate Efficacy and Safety of Ribociclib With Endocrine Therapy as Adjuvant Treatment in Patients With HR+/HER2- Early Breast Cancer | ClinicalTrials.gov)

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.

As outlined in **Section 3d**, the ongoing clinical trial NATALEE studies the effectiveness (how well a treatment works) and safety (side effects) of ribociclib as a treatment for HR-positive, HER2-negative early breast cancer at high risk of recurrence.

NATALEE trial results

Results from NATALEE show that ribociclib plus AI therapy (compared to AI therapy alone) lowered the risk of invasive cancer recurrence in patients with early breast cancer by over a quarter (28.5%). At 4 years into treatment, 88.5% of patients receiving ribociclib plus AI therapy were alive, free of invasive breast cancer or any other breast cancer compared to 83.6% of patients receiving AI therapy alone.[30] Additionally, patients receiving ribociclib plus AI therapy were 28.5% less likely to experience a distant disease recurrence (away from the breast) than patients receiving AI therapy alone.[30]

For the subgroup of patients in NATALEE with node-positive disease, ribociclib plus AI therapy (compared to AI therapy alone) lowered the risk of invasive cancer recurrence in patients with early breast cancer by 26.9%. Similarly, for the subgroup of patients in NATALEE with node-negative disease, ribociclib plus AI therapy (compared to AI therapy alone) lowered the risk of invasive cancer recurrence in patients with early breast cancer by 33.4%, although notably this

result was not **statistically significant.**[30]

These results show that ribociclib plus AI therapy is effective in reducing breast cancer recurrence (by over a quarter) among patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence,[30] and that results are generally similar across patients with different nodal statuses.

More results on the effectiveness of ribociclib plus AI therapy can be found in **Document B, Section 2.6.**

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.

The impact of ribociclib on patient quality of life

At different timepoints throughout NATALEE, patients were asked to answer questions about their quality of life using several different questionnaires.

The results from the questionnaires showed that the addition of ribociclib to the treatment of patients with early breast cancer did not meaningfully impact patients' quality of life. Although there was an overall decline in patients' questionnaire scores over time, the overall change in wellbeing was similar between the two groups of patients in NATALEE (those receiving ribociclib plus AI therapy and those receiving AI therapy alone). This means that ribociclib provided a clinical benefit (i.e. it reduced the risk of breast cancer recurrence; **Section 3e**) but did not harm patient wellbeing.

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.

Side effects

Every medicine has its own side effects and the same medicine can produce different reactions in different people. However, safety results from NATALEE found that ribociclib plus AI therapy is well tolerated among patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence.[30] No new side effects (i.e. side effects other than those already known from use among patients with advanced breast cancer) were identified during

NATALEE.[30]

Some very common side effects of ribociclib (known from use among patients with advanced breast cancer) include:[31]

- Tiredness
- Pale skin
- Sore throat, runny nose and fever
- Painful and frequent need to urinate
- Reduced appetite
- Headache
- Dizziness or light headedness
- Shortness of breath or difficulty breathing
- Cough
- Nausea (feeling sick)
- Diarrhoea

Always tell your doctor, pharmacist or nurse if you experience any severe side effects while taking ribociclib.

Managing side effects

If patients experience severe or intolerable side effects while taking ribociclib, the dose of ribociclib can be reduced, treatment can be temporarily stopped and restarted when appropriate (**dose interruption**), or treatment can be stopped completely (**treatment discontinuation**).

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

Ribociclib would address a broad population of patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence

Many patients receiving currently available treatments for early breast cancer experience disease recurrence. The fear of cancer recurrence negatively affects the emotional wellbeing of patients with breast cancer and their families, as recurrent cancer (cancer that has come back) may progress to advanced or metastatic cancer which is incurable and has a lower rate of survival. The introduction of abemaciclib (the newest treatment option for early breast cancer; **Section 2c**) is anticipated to reduce disease recurrence among patients whose breast cancer is at a high risk of recurring and has spread to nearby lymph nodes and has extra high-risk features. However, abemaciclib is not suitable for a large proportion of the wider population of patients with HR-positive, HER2-negative early breast cancer patients.

There is a need for breast cancer treatments that lower the risk of recurrence and are available to a larger proportion of patients. If approved, ribociclib has the potential to address this unmet need as it is suitable for a wider population of patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence, including for patients whose cancer has not spread to nearby lymph nodes.

Ribociclib in combination with AI therapy is more effective than AI therapy alone

In NATALEE, ribociclib plus AI therapy was shown to be more effective (in reducing disease recurrence) than the standard treatment of AI therapy alone (Section 3e). The risk of experiencing disease recurrence was reduced by over a quarter among patients receiving ribociclib plus AI therapy (compared to those receiving AI therapy alone). Treatment with ribociclib plus AI therapy was also associated with a lower chance of the cancer becoming more advanced and spreading to other parts of the body.[30]

Additionally, the questionnaire responses collected during NATALEE showed that the quality of life of patients in both treatment groups was similar. This highlighted that the addition of ribociclib to AI therapy did not harm patient wellbeing.

If approved, ribociclib would provide a new, well-tolerated, effective treatment option for a large proportion of patients with HR-positive, HER2-negative early breast cancer at high risk of recurring.

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

Ribociclib is generally well-tolerated and effective in reducing cancer recurrence in patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence. However, as with all medicines, ribociclib can cause some side effects. Very common side effects include tiredness, sore throat, reduced appetite, headache and shortness of breath which may impact patients' quality of life.[31] However, side effects associated with ribociclib are usually manageable.

Additionally, ribociclib must be taken on days 1 to 21 of a 28-day cycle for a total of 3 years (unless treatment is discontinued sooner due to severe side effects or cancer progression),[28] which some patients may consider an inconvenience. However, ribociclib is taken as a tablet, so patients do not need to travel to hospital to receive treatment.

3i) 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.

For this submission, an **economic model** was designed and built to reflect the key features of the breast cancer pathway in the UK and assess whether ribociclib in combination with AI therapy represents a cost-effective use of NHS resources. The model assessed ribociclib in combination with AI across all four populations addressed in this submission:

1) Population 1: *All* patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence
2) Population 2: Patients with *node-positive* HR-positive, HER2-negative early breast cancer at high risk of recurrence
3) Population 3: Patients with *node-negative* HR-positive, HER2-negative early breast cancer at high risk of recurrence
4) Population 4: Patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence, *eligible for abemaciclib*

The economic model compared the costs and benefits of treatment with ribociclib in combination with AI therapy against other existing treatments. The main existing treatment that ribociclib plus AI therapy was compared against within the economic model was standard hormone therapy. In addition, ribociclib plus AI therapy was compared against the only available targeted therapy called abemaciclib plus hormone therapy. This comparison was made in Population 4 only, i.e., the subgroup of patients with HR-positive, HER-negative early breast cancer at high risk of recurrence who are eligible for abemaciclib.

How the economic model reflects the condition

The economic model included a number of health states to reflect the breast cancer pathway in the UK. Patients entered the model and were assumed to receive treatment for their early breast cancer. The benefits and costs associated with this treatment were then added together for either ribociclib plus AI therapy, hormone therapy alone, or abemaciclib plus hormone therapy.

Following treatment in the economic model, patients could progress into other health states of the economic model which reflect advanced breast cancer. Here they were assumed to receive different treatments and the benefits and costs of these treatments were also added together.

Modelling the effectiveness and safety of treatment with ribociclib

For ribociclib plus AI therapy, and standard hormone therapy, the results of NATALEE were used to inform the economic model. The main result from the trials that was used in the model was the risk of invasive disease-free survival i.e. the number of patients in each treatment group who are alive and free of any invasive breast cancer (cancer that has spread into surrounding breast tissue) or any other type of cancer. This was the main result used in the economic model because it was considered relevant to what would be considered a

successful outcome when treating patients with early breast cancer in clinical practice.

For abemaciclib plus hormone therapy, results from a clinical trial that studied how well abemaciclib plus hormone therapy works in patients with early breast cancer were used. This trial is called monarchE. More details of the monarchE trial can be found here:

1) ClinicalTrials.gov (MonarchE) (Study Details | Endocrine Therapy With or Without Abemaciclib (LY2835219) Following Surgery in Participants With Breast Cancer (monarchE) | ClinicalTrials.gov)

In order to compare the results for ribociclib plus AI therapy from NATALEE with the results for abemaciclib plus hormone therapy from monarchE, a statistical analysis called a '**matching-adjusted indirection comparison**' was conducted. This type of analysis tries to align the patient populations from the two trials to make a fair comparison between the two treatments. In the economic model, ribociclib plus hormone therapy and abemaciclib plus hormone therapy were assumed to be equivalent in terms of efficacy.

Modelling how treatment with ribociclib affects quality of life

An improvement in quality of life was modelled based on which health states of the economic model patients were in. This reflects the fact that the mental and emotional impact of breast cancer is likely increased if a patient progresses to advanced breast cancer. The quality of life data that informed the model were from NATALEE.

Modelling how the costs of treatment with ribociclib differ compared with existing treatments

Various costs were included in the model for the different treatments. These costs included:

1) The cost of the medicines themselves and how much it costs to administer them
2) The cost of starting treatment and the cost of monitoring the patients during treatment
3) The cost of side effects that happen during treatment
4) The cost of the medicines received, as well as the administration, and the costs of monitoring, if the cancer progresses to advanced or metastatic cancer
5) The costs associated with dying

Uncertainty

There are various assumptions that had to be made in the economic model. Information on these assumptions can be found in **Document B, Section B.3.9.2**. Variations of other inputs in the model were also tested and the results of these tests are explained in **Document B, Section B.3.11.**

Cost effectiveness results

Based on the modelling inputs and assumptions from Novartis, treatment with ribociclib plus AI therapy was estimated to be associated with higher health benefits (or '**quality-adjusted life years' [QALYs]**) at a higher cost than hormone therapy alone and abemaciclib plus hormone therapy. However, it is important to acknowledge that these results are estimations from the Company and do not incorporate the confidential discounted price that may be available for some of the medicines costed within the model.

3j) 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)

Ribociclib is an innovative treatment which would represent an important advancement in the treatment of early breast cancer

Breast cancer is a condition that can have a significant effect on patients' quality of life.[8, 32] The fear of cancer recurrence (the cancer coming back) negatively affects the emotional wellbeing of patients with breast cancer and their families, as recurrent cancer is often incurable and has a lower rate of survival.[32] Even with the most current treatment options for early breast cancer after surgery, the risk of breast cancer recurrence remains high. The newer treatment option (abemaciclib) is expected to reduce the risk of recurrence, but is not suitable for a large population of patients with early breast cancer, in particular those with cancer that has not spread to nearby lymph nodes.[3, 33] There is a need for a new well-tolerated breast cancer treatment which lowers the risk of breast cancer recurrence and is available to a larger population of patients.

If recommended, ribociclib would be the second medicine available to patients with early breast cancer that blocks CDK 4 and CDK 6 proteins (**Section 3a**). These new medicines are targeted therapies and work in combination with existing hormone therapy such as AI therapy (**Section 3b**). Importantly, ribociclib would be suitable for a much bigger population of patients with early breast cancer than abemaciclib (the other blocker of CDK4 and CDK 6 that is currently available). This means that more patients would benefit from this new type of medicine.

Data from the NATALEE trial (**Section 3e**) shows that ribociclib plus AI therapy is more effective than AI therapy alone at preventing disease recurrence.[30] Ribociclib is also generally well-tolerated with manageable side effects.

3k) 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

There are no equality issues that are anticipated with the use of ribociclib in early breast cancer. Ribociclib is anticipated to be used in both women and men with early breast cancer.

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.

Further information on breast cancer:

- Breast Cancer UK (https://www.breastcanceruk.org.uk/)
- Cancer Research UK (https://www.cancerresearchuk.org/about-cancer/breast-cancer)
- Macmillan Cancer Support (https://www.macmillan.org.uk/cancer-information-and-support/breast-cancer)

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

4b) Glossary of terms

This glossary explains terms highlighted in **blue bold text** in this summary of information for patients.

Term	Definition
Adjuvant	A treatment given after surgery.
Advanced or metastatic breast cancer	Breast cancer that has spread from the breast to another part of the body.
Aromatase inhibitor	A **hormone therapy** medicine which inhibits the **protein** aromatase. Aromatase inhibitors reduce the level of oestrogen circulating the body, meaning there is less oestrogen to stimulate growth of **HR-positive** cancer cells.
Biopsy	A biopsy is a medical procedure where a small sample of tissue is taken from your body. This tissue is then examined under a

	microscope to check for cancer cells or other abnormalities.
Breast cancer screening	Regular screening (using a **mammogram**) of healthy women for breast cancer. This increases the chance of finding breast cancer at an early stage when it is more likely to be treated successfully.
Chemotherapy	A type of cancer therapy that uses drugs to kill cancer cells.
Clinical trial	A type of research study that compares how well one treatment works against other treatment(s).
Cyclin dependent kinases 4 and 6 (CDK4 and CDK6)	**Proteins** involved in regulating cell division.
Dose interruption	Patients may stop taking the treatment temporarily (for example to recover from any side effects they are experiencing), then restart the treatment when appropriate.
Early breast cancer	The cancer has not spread away from the breast, and therefore is only present in the breast tissue and surrounding **lymph nodes**.
Economic model	An economic model is a framework that is a simplified representation of the real world and aims to assess the differences in costs and benefits between medicines.
Effectiveness	How well a treatment works.
European Medicines Agency (EMA)	The regulatory body that evaluates, approves and supervises medicines throughout the European Union.
Fatigue	Feeling very tired, exhausted and lacking energy. It can be a symptom of the cancer itself or a **side effect** of treatment.
Grade	How abnormal the breast cancer cells look under a microscope.
Hormones	Chemical substances that carry messages within the body to help coordinate different bodily functions.
Hormone therapy	Therapies commonly used to treat breast cancer that work by altering the production or activity of particular **hormones** in the body.
Hormone receptor positive (HR-positive)	**Proteins** on the surface of some cancer cells to which **hormones**, such as oestrogen or progesterone, can bind. Cancer cells with hormone receptors are said to be hormone receptor positive (HR-positive).
Human epidermal growth factor 2	A **protein receptor** on the surface of cells. Excess HER2 encourages cancer cells to divide and grow.

(HER2)	
Human epidermal growth factor receptor 2 negative (HER2-negative)	HER2-negative breast cancer means the cancer cells do not have high levels of **HER2** on their surface.
Immune system	A complex network of cells, tissues, organs and the substances they make. The immune system helps the body fight infections and other diseases.
Invasive breast cancer	Breast cancer that has spread into surrounding breast tissue.
Lymph nodes (also called nodes)	Small structures in the body that trap germs and abnormal cells. Lymph nodes are found in the neck, armpit and groin.
Mammogram	A low dose x-ray image of the breast used to detect cancer.
Marketing authorisation	The approval by a regulatory body that allows a medicine to be given to patients in a particular country.
Matching-adjusted indirection comparison	A type of statistical analysis that compares the effectiveness of treatments. The matching relates to alignment of the patient populations from the two trials to make a fair comparison between the two treatments.
Nodal status	Whether a patient's cancer has not spread to nearby lymph nodes (node-negative) or has spread to nearby lymph nodes or other organs (node-positive).
NATALEE	A **phase 3 clinical trial** investigating the **effectiveness** and safety of ribociclib plus **AI** therapy for treating **early breast cancer**.
Nausea	Sickness in the stomach with an urge to vomit.
Neoadjuvant	Treatment given before surgery.
Phase 3	This is a type of **clinical trial** that tests the safety and **effectiveness** of a new treatment compared with a standard treatment. For example, it evaluates which group of patients in the trial has better survival rates or fewer **side effects**.
Population 1	The main population of patients being addressed in this submission. The definition of this population aligns with the anticipated marketing authorisation for ribociclib and the patients eligible for the NATALEE trial.
Population 2	This population represents patients who would have been eligible for the NATALEE trial with node-positive disease.

Population 3	This population represents patients who would have been eligible for the NATALEE trial with node-negative disease.
Population 4	This population represents patients who are currently eligible for abemaciclib, as per the recommendation in NICE TA810.[34]
Primary breast tumour	The tumour where the cancer first started growing.
Proteins	Structures inside all cells of the body that are important for many activities, including growth and repair.
Quality-adjusted life years	The quality-adjusted life year is a summary outcome measure used to quantify the effectiveness of a particular medicine. QALYs have been designed to combine the impact of gains in quality of life and in quantity of life (i.e. life expectancy) associated with a particular medicine.
Quality of life	The overall enjoyment of life. Many **clinical trials** assess the effects of a condition and its treatment on the quality of life. These studies measure aspects of an individual's sense of well-being and their ability to carry out activities of daily living.
Radiotherapy	A type of cancer therapy that uses radiation to kill cancer cells.
Receptors	A **protein** structure on the surface of cells that **hormones** or **proteins** can attach to.
Risk of recurrence	The breast cancer may come back (recur) after the initial treatment has been completed.
Side effect (also called adverse event)	An unexpected medical problem that arises during treatment with a medicine or other therapy. Side effects may be mild, moderate, or severe.
Stage	A description of the size and spread of a cancer.
Statistical significance	A way of determining if the results show a true effect rather than happening by random chance.
Targeted treatments	Drugs that work by 'targeting' the differences between a cancer cell and normal cell that help cancer cells survive and grow. As these therapies target cancer cells specifically, they limit damage to healthy parts of the body.
Tolerated	The ability to put up with the **side effects** of treatment.
Treatment cycle	Many cancer treatments are given in cycles. Each cycle is often divided into a period where treatment is received, followed by a period of rest from treatment to allow the body to recover from the

	side effects of treatment. The length of each cycle and the split between treatment and rest periods can depend on the type of cancer, where it is in the body and if it has spread and where to.
Treatment discontinuation	If **side effects** are too severe or the treatment is not working, the patient may decide to stop taking the treatment, known as treatment discontinuation.
Ultrasound	A imaging method which captures live images from inside the body using sound waves.

4c) References

1. National Cancer Institute. Hormone therapy for breast cancer. Available from: https://www.cancer.gov/types/breast/breast-hormone-therapy-fact-sheet. Accessed: 1 November 2023.
2. American Cancer Society. Breast Cancer Facts & Figures 2022-2024. 2022. Available from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/2022-2024-breast-cancer-fact-figures-acs.pdf. Accessed: 9 September 2024.
3. Pan H, Gray R, Braybrooke J, et al. 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. N Engl J Med 2017;377:1836-1846.
4. Gomis RR, Gawrzak S. Tumor cell dormancy. Mol Oncol 2017;11:62-78.
5. Łukasiewicz S, Czeczelewski M, Forma A, et al. Breast Cancer-Epidemiology, Risk Factors, Classification, Prognostic Markers, and Current Treatment Strategies-An Updated Review. Cancers (Basel) 2021;13:4287.
6. Cancer Research UK. Breast cancer statistics. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer. Accessed: 18 April 2023.
7. Cancer Research UK. Proportion Diagnosed by Stage (stacked chart). 2021 Available from: https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/. Accessed: 7 August 2023.
8. Marschner N, Zacharias S, Lordick F, et al. Association of Disease Progression With Health-Related Quality of Life Among Adults With Breast, Lung, Pancreatic, and Colorectal Cancer. JAMA Netw Open 2020;3:e200643.
9. Cancer Research UK. Side effects of hormone therapy in women. 2021. Available from: https://www.cancerresearchuk.org/about-cancer/treatment/hormone-therapy/side-effects-women. Accessed: 23rd November 2023.
10. Macmillan Cancer Support. Abemaciclib (Verzenios®). 2023. Available from: https://www.macmillan.org.uk/cancer-information-and-support/treatments-and-drugs/abemaciclib. Accessed 23 November 2023.
11. Novartis. Shining a spotlight on the impact of breast cancer recurrence. 2024. Available from: https://www.novartis.com/uk-en/sites/novartis_uk/files/Shining%20a%20spotlight%20on%20the%20impact%20of%20breast%20cancer%20recurrence%20-%20April%202024.pdf Accessed: 3 September 2024.
12. University of Oxford. Cancer costs the UK economy £15.8bn a year. 2012. Available from: https://www.ox.ac.uk/news/2012-11-07-cancer-costs-uk-economy-%C2%A3158bn-year. Accessed: 1 April 2023.

13. Mohammadpour S, Soleimanpour S, Javan-Noughabi J, et al. A systemmatic literature review on indirect costs of women with breast cancer. Cost Eff Resour Alloc 2022;20:68.
14. Seweryn M, Banas T, Augustynska J, et al. The Direct and Indirect Costs of Breast Cancer in Poland: Estimates for 2017-2019. Int J Environ Res Public Health 2022;19.
15. Chiu K, MacEwan JP, May SG, et al. Estimating Productivity Loss from Breast and Non-Small-Cell Lung Cancer among Working-Age Patients and Unpaid Caregivers: A Survey Study Using the Multiplier Method. MDM Policy Pract 2022;7:23814683221113846.
16. NHS Digital. NHS Breast Screening Programme, England 2021-22. 2023. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/breast-screening-programme/england---2021-22/mainreport2122-copy#top. Accessed: 1 July 2023.
17. Macmillan Cancer Support. Breast cancer. 2018. Available from: https://www.macmillan.org.uk/cancer-information-and-support/breast-cancer. Accessed: 23 November 2023.
18. National Cancer Institute. Early-stage breast cancer. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/early-stage-breast-cancer. Accessed: 18 April 2023.
19. Macmillan Cancer Support. Staging and grading of breast cancer. 2018. Available from: https://www.macmillan.org.uk/cancer-information-and-support/breast-cancer/staging-and-grading-of-breast-cancer. Accessed: 23 November 2023.
20. NICE. NG101. Early and locally advanced breast cancer: diagnosis and management. 2018. Available from: https://www.nice.org.uk/guidance/ng101/resources/early-and-locally-advanced-breast-cancer-diagnosis-and-management-pdf-66141532913605. Accessed: April 2023, 2018.
21. Tarantino P, Rugo HS, Curigliano G, et al. 245P Characteristics of real-world (RW) NATALEE and monarchE eligible populations: A US electronic health records (EHR) database analysis. Annals of Oncology 2024;35:S317-S318.
22. Verrill M, Wardley AM, Retzler J, et al. Health-related quality of life and work productivity in UK patients with HER2-positive breast cancer: a cross-sectional study evaluating the relationships between disease and treatment stage. Health Qual Life Outcomes 2020;18:353.
23. Chirgwin JH, Giobbie-Hurder A, Coates AS, et al. Treatment Adherence and Its Impact on Disease-Free Survival in the Breast International Group 1-98 Trial of Tamoxifen and Letrozole, Alone and in Sequence. J Clin Oncol 2016;34:2452-9.
24. John S, Broggio J. Cancer survival in England - adults diagnosed (2013-2017 edition). Office for National Statistics 2019. Available from:https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed. Accessed: 11 October 2024
25. Obaidi JG, Al-Atiyyat NM. Quality of life among primary caregivers of women with breast cancer: A review. Middle East Journal of Cancer 2013;4:45-49.
26. Wagner CD, Bigatti SM, Storniolo AM. Quality of life of husbands of women with breast cancer. Psychooncology 2006;15:109-20.
27. Cancer Research UK. Ribociclib (Kisqali). 2020. Available from: https://www.cancerresearchuk.org/about-cancer/treatment/drugs/ribociclib. Accessed: 23 November 2023.

28. European Medicines Agency. Kisqali, INN-ribociclib. Annex I: Summary of Product Characteristics (SmPC). 2017. Available from: https://www.ema.europa.eu/en/documents/product-information/kisqali-epar-product-information_en.pdf. Accessed: 22 October 2024.
29. ClinicalTrials.gov. A Trial to Evaluate Efficacy and Safety of Ribociclib With Endocrine Therapy as Adjuvant Treatment in Patients With HR+/HER2- Early Breast Cancer (NATALEE). Available from: https://clinicaltrials.gov/ct2/show/NCT03701334?term=NATALEE&draw=2&rank=1. 2023.
30. Fasching PA, Stroyakovskiy D, Yardley D, et al. LBA13 Adjuvant Ribociclib Plus Nonsteroidal Aromatase Inhibitor in Patients With HR+/HER2− Early Breast Cancer: 4-Year Outcomes From the NATALEE Trial. Annals of Oncology 2024;35:S1207.
31. Electronic Medicines Compendium. Package leaflet: Information for the patient: Kisqali® 200 mg film-coated tablets. 2024. Available from: https://www.medicines.org.uk/emc/files/pil.8110.pdf. Accessed: 15 October 2024.
32. Park J, Rodriguez JL, O'Brien KM, et al. Health-related quality of life outcomes among breast cancer survivors. Cancer 2021;127:1114-1125.
33. McGuinness S, Hughes L, Moss-Morris R, et al. Adherence to adjuvant endocrine therapy among White British and ethnic minority breast cancer survivors in the United Kingdom. Eur J Cancer Care (Engl) 2022;31:e13722.
34. NICE. Abemaciclib with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence [TA810]. Available from: https://www.nice.org.uk/guidance/ta810. Accessed: 11 October 2024., 2022.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Ribociclib with an aromatase inhibitor for adjuvant treatment of hormone receptor-positive, HER2-negative early breast cancer [ID6153]

Clarification questions

November 2024

File name	Version	Contains confidential information	Date
ID6153_Ribociclib_NICE_Clarification questions response v3.0 [REDACTED]	3.0	No	12th December 2024

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Population

A1. Please confirm that the NATALEE trial Population 4 (population evaluated in TA810), the 'NATALEE selected population' (CS, Table 31) and the 'NATALEE selected unweighted population' (CS, Table 32) refer to the same population. If not, please explain the differences.

Yes, Population 4 (the population evaluated in TA810), the "NATALEE selected population" (Company Submission [CS], Table 31) and the "NATALEE selected unweighted population" (CS, Table 32) refer to the same population. This population, referred to in the CS as Population 4 (node-positive high-risk eligible for abemaciclib), represents the patient population appraised in NICE TA810,[1] which is defined in Section B.1.1 of the CS.

However, following the EAG request in Clarification Question (CQ) B1 for a direct evidence comparison of ribociclib plus AI versus ET within Population 4, and to distinguish between this population and the weighted Population 4 derived from the matched adjusted indirect comparison (MAIC), the Company have now renamed Population 4 into Population 4A and Population 4B as follows:

- **Population 4A:** The previous "NATALEE selected unweighted population" reported in the CS Table 31 is now referred to as "Population 4A (unweighted node-positive high-risk eligible for abemaciclib)". This population is used for the direct evidence comparison requested by the EAG in CQ B1, and represents the NATALEE patient population who are eligible for abemaciclib, but have not had their baseline characteristics weighted to match monarchE Cohort 1.
- **Population 4B:** The previous "NATALEE selected, weighted population" reported in the CS Table 32 is now referred to as "Population 4B (weighted node-positive high-risk eligible

for abemaciclib)". This population represents the NATALEE patient population who are eligible for abemaciclib, with patient baseline characteristics weighted to match monarchE Cohort 1 via the MAIC.

A2. Priority question. Please provide NATALEE trial baseline characteristics, iDFS, RFS, DDFS and OS results (for the comparison of ribociclib + AI versus AI) for the following populations:

- **Abemaciclib + AI eligible population:** i.e., NATALEE trial Population 4 (population evaluated in TA810)

Baseline characteristics

The abemaciclib plus AI eligible population: i.e., NATALEE trial Population 4 (population evaluated in TA810) referred to by the EAG in this question is herein referred to by the Company as Population 4A (unweighted node-positive high-risk eligible for abemaciclib). The baseline characteristics for Population 4A (unweighted node-positive high-risk eligible for abemaciclib) can be found in the reference pack accompanying this response, in the zipped folder titled "NATALEE Population 4A Additional Resources".

Invasive disease-free survival (iDFS)

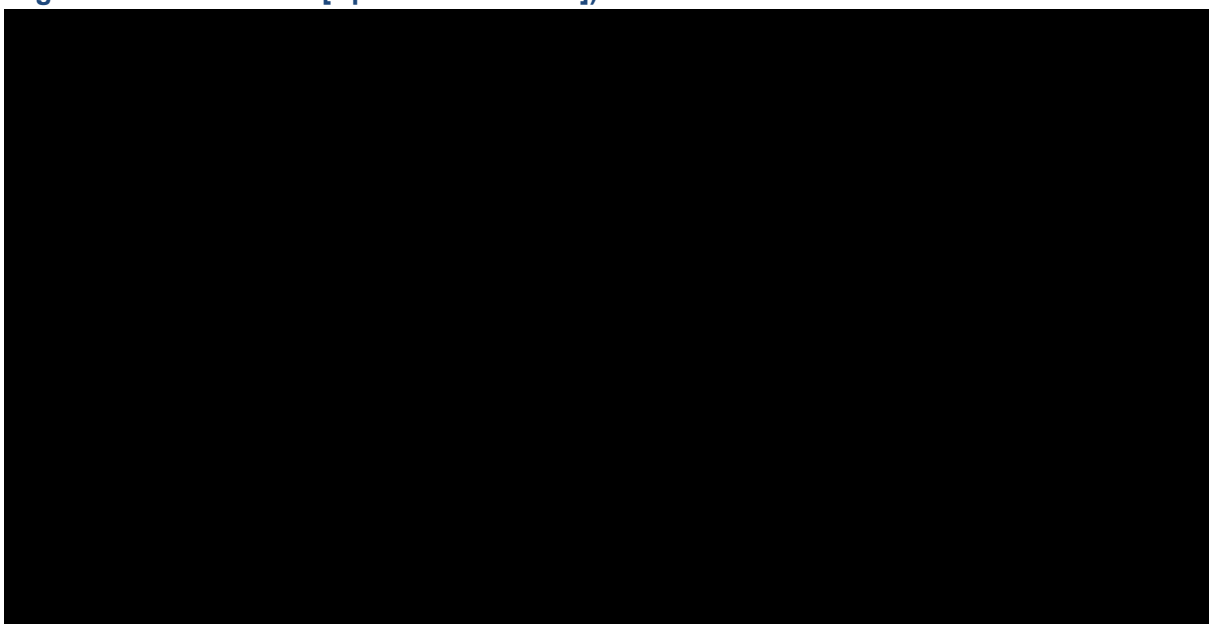
The iDFS results for the comparison of ribociclib plus AI versus AI in Population 4A (unweighted node-positive high-risk eligible for abemaciclib), derived directly from the NATALEE trial, are presented in Table 1, and the corresponding Kaplan-Meier curve is presented in Figure 1.

Table 1: Summary of iDFS in Population 4A (unweighted node-positive high-risk eligible for abemaciclib [April 2024 data cut]) from NATALEE

	Ribociclib plus AI (N=1,658)	AI (N=1,649)
Number of events, n (%)	[redacted]	[redacted]
p-value log-rank[a]	[redacted]	
HR[b] (95% CI)	[redacted]	

Footnotes: [a] 1-sided p-value for log-rank test stratified by premenopausal women and men vs postmenopausal women, anatomic stage group II vs anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs no) and North America/Western Europe/Oceania vs rest of world.
[b] Hazard rate in group AI + ribociclib versus hazard rate in group AI only is computed using the Cox proportional hazards model with treatment as a single covariate and premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world as stratification factors.
The group ET only is the reference in the hazard ratio calculation.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; HR: hazard ratio; iDFS: invasive disease-free survival.
Source: Novartis Data on File (2024).[2]

Figure 1: Kaplan-Meier plot for iDFS in Population 4A (unweighted node-positive high-risk eligible for abemaciclib [April 2024 data cut]) from NATALEE



Footnotes: As only AI therapies were received in the NATALEE trial, the "ET" component of the intervention and comparator arm represents AI.
P-value is obtained from the one-sided log-rank test stratified by premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III,
prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world.
Hazard ratio (95% CI) is obtained by Cox PH model stratified by premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III,
prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; iDFS: invasive disease-free survival; ET: endocrine therapy; HR: hazard ratio.
Source: Novartis Data on File (2024).[2]

Recurrence-free survival (RFS)

The RFS results for the comparison of ribociclib plus AI versus AI in Population 4A (unweighted node-positive high-risk eligible for abemaciclib), derived directly from the NATALEE trial, are presented in Table 2, and the corresponding Kaplan-Meier curve is presented in Figure 2.

Table 2: Summary of RFS in Population 4A (unweighted node-positive high-risk eligible for abemaciclib [April 2024 data cut]) from NATALEE

	Ribociclib plus AI (N=1,658)	AI (N=1,649)
Number of events, n (%)	[redacted]	[redacted]
p-value log-rank[a]	[redacted]	
HR[b] (95% CI)	[redacted]	

Footnotes: [a] 1-sided p-value for log-rank test stratified by premenopausal women and men vs postmenopausal women, anatomic stage group II vs anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs no) and North America/Western Europe/Oceania vs rest of world.
[b] Hazard rate in group AI + ribociclib versus hazard rate in group AI only is computed using the Cox proportional hazards model with treatment as a single covariate and premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world as stratification factors.
The group ET only is the reference in the hazard ratio calculation.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; HR: hazard ratio; RFS: recurrence-free survival.
Source: Novartis Data on File (2024).[2]

Figure 2: Kaplan-Meier plot for RFS in Population 4A (unweighted node-positive high-risk eligible for abemaciclib [April 2024 data cut]) from NATALEE

Footnotes: As only AI therapies were received in the NATALEE trial, the "ET" component of the intervention and comparator arm represents AI.
P-value is obtained from the one-sided log-rank test stratified by premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III,
prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world.
Hazard ratio (95% CI) is obtained by Cox PH model stratified by premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III,
prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; RFS: recurrence-free survival.
Source: Novartis Data on File (2024).[2]

Distant disease-free survival (DDFS)

The DDFS results for the comparison of ribociclib plus AI versus AI in Population 4A (unweighted node-positive high-risk eligible for abemaciclib), derived directly from the NATALEE trial, are presented in Table 3, and the corresponding Kaplan-Meier curve is presented in Figure 3.

Table 3: Summary of DDFS in Population 4A (unweighted node-positive high-risk eligible for abemaciclib [April 2024 data cut]) from NATALEE

	Ribociclib plus AI (N=1,658)	AI (N=1,649)
Number of events, n (%)	[redacted]	[redacted]
p-value log-rank[a]	[redacted]	
HR[b] (95% CI)	[redacted]	

Footnotes: [a] 1-sided p-value for log-rank test stratified by premenopausal women and men vs postmenopausal women, anatomic stage group II vs anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs no) and North America/Western Europe/Oceania vs rest of world.
[b] Hazard rate in group AI + ribociclib versus hazard rate in group AI only is computed using the Cox proportional hazards model with treatment as a single covariate and premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world as stratification factors.
The group ET only is the reference in the hazard ratio calculation.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; DDFS: distant disease-free survival; HR: hazard ratio.
Source: Novartis Data on File (2024).[2]

Figure 3: Kaplan-Meier plot for DDFS in Population 4A (unweighted node-positive high-risk eligible for abemaciclib [April 2024 data cut]) from NATALEE

Footnotes: As only AI therapies were received in the NATALEE trial, the "ET" component of the intervention and comparator arm represents AI.
P-value is obtained from the one-sided log-rank test stratified by premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world.
Hazard ratio (95% CI) is obtained by Cox PH model stratified by premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; DDFS: distant disease-free survival ET: endocrine therapy; HR: hazard ratio.
Source: Novartis Data on File (2024).[2]

Overall survival (OS)

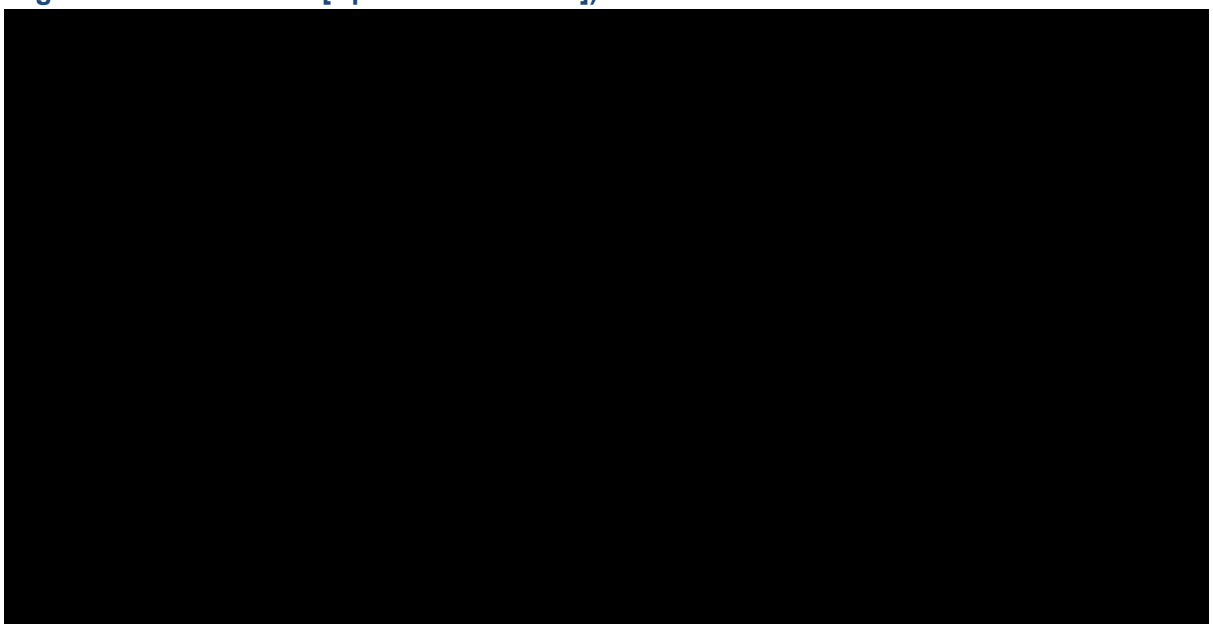
The OS results for the comparison of ribociclib plus AI versus AI in Population 4A (unweighted node-positive high-risk eligible for abemaciclib), derived directly from the NATALEE trial, are presented in Table 4, and the corresponding Kaplan-Meier curve is presented in Figure 4.

Table 4: Summary of OS in Population 4A (unweighted node-positive high-risk eligible for abemaciclib [April 2024 data cut]) from NATALEE

	Ribociclib plus AI (N=1,658)	AI (N=1,649)
Number of events, n (%)	[redacted]	[redacted]
p-value log-rank[a]	[redacted]	
HR[b] (95% CI)	[redacted]	

Footnotes: [a] 1-sided p-value for log-rank test stratified by premenopausal women and men vs postmenopausal women, anatomic stage group II vs anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs no) and North America/Western Europe/Oceania vs rest of world.
[b] Hazard rate in group AI + ribociclib versus hazard rate in group AI only is computed using the Cox proportional hazards model with treatment as a single covariate and premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world as stratification factors.
The group ET only is the reference in the hazard ratio calculation.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; HR: hazard ratio; OS: overall survival.
Source: Novartis Data on File (2024).[2]

Figure 4: Kaplan-Meier plot for OS in Population 4A (unweighted node-positive high-risk eligible for abemaciclib [April 2024 data cut]) from NATALEE



Footnotes: As only AI therapies were received in the NATALEE trial, the "ET" component of the intervention and comparator arm represents AI.
P-value is obtained from the one-sided log-rank test stratified by premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III,
prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world.
Hazard ratio (95% CI) is obtained by Cox PH model stratified by premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III,
prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; OS: overall survival.
Source: Novartis Data on File (2024).[2]

- **abemaciclib + AI ineligible population:** i.e., NATALEE trial Population 1 excluding NATALEE trial Population 4 (population evaluated in TA810)

Baseline characteristics

The "abemaciclib plus AI ineligible population" (i.e., NATALEE trial Population 1 excluding NATALEE trial Population 4 [population evaluated in TA810]) referred to by the EAG in this question is herein referred to by the Company as Population 5 (NATALEE high-risk ineligible for abemaciclib). The baseline characteristics for Population 5 (NATALEE high-risk ineligible for abemaciclib) can be found in the reference pack accompanying this response, in the zipped folder titled "NATALEE Population 5 Additional Resources".

Invasive disease-free survival (iDFS)

The iDFS results for the comparison of ribociclib plus AI versus AI in Population 5 (NATALEE high-risk ineligible for abemaciclib), derived directly from the NATALEE trial, are presented in Table 5, and the corresponding Kaplan-Meier curve is presented in Figure 5.

Table 5: Summary of iDFS in Population 5 (NATALEE high-risk ineligible for abemaciclib [April 2024 data cut]) from NATALEE

	Ribociclib plus AI (N=891)	AI (N=903)
Number of events, n (%)	[redacted]	[redacted]
p-value log-rank[a]	[redacted]	
HR[b] (95% CI)	[redacted]	

Footnotes: [a] 1-sided p-value for log-rank test stratified by premenopausal women and men vs postmenopausal women, anatomic stage group II vs anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs no) and North America/Western Europe/Oceania vs rest of world.
[b] Hazard rate in group AI + ribociclib versus hazard rate in group AI only is computed using the Cox proportional hazards model with treatment as a single covariate and premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world as stratification factors.
The group ET only is the reference in the hazard ratio calculation.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; HR: hazard ratio; iDFS: invasive disease-free survival.
Source: Novartis Data on File (2024).[2]

Figure 5: Kaplan-Meier plot for iDFS in Population 5 (NATALEE high-risk ineligible for abemaciclib [April 2024 data cut]) from NATALEE

[redacted]

Footnotes: As only AI therapies were received in the NATALEE trial, the "ET" component of the intervention and comparator arm represents AI.
P-value is obtained from the one-sided log-rank test stratified by premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world.
Hazard ratio (95% CI) is obtained by Cox PH model stratified by premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; iDFS: invasive disease-free survival; ET: endocrine therapy; HR: hazard ratio.
Source: Novartis Data on File (2024).[2]

Recurrence-free survival (RFS)

The RFS results for the comparison of ribociclib plus AI versus AI in Population 5 (NATALEE high-risk ineligible for abemaciclib), derived directly from the NATALEE trial, are presented in Table 6, and the corresponding Kaplan-Meier curve is presented in Figure 6.

Table 6: Summary of RFS in Population 5 (NATALEE high-risk ineligible for abemaciclib [April 2024 data cut]) from NATALEE

	Ribociclib plus AI (N=891)	AI (N=903)
Number of events, n (%)	[redacted]	[redacted]
p-value log-rank[a]	[redacted]	
HR[b] (95% CI)	[redacted]	

Footnotes: [a] 1-sided p-value for log-rank test stratified by premenopausal women and men vs postmenopausal women, anatomic stage group II vs anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs no) and North America/Western Europe/Oceania vs rest of world.
[b] Hazard rate in group AI + ribociclib versus hazard rate in group AI only is computed using the Cox proportional hazards model with treatment as a single covariate and premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world as stratification factors.
The group ET only is the reference in the hazard ratio calculation.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; HR: hazard ratio; RFS: recurrence-free survival.
Source: Novartis Data on File (2024).[2]

Figure 6: Kaplan-Meier plot for RFS in Population 5 (NATALEE high-risk ineligible for abemaciclib [April 2024 data cut]) from NATALEE

Footnotes: As only AI therapies were received in the NATALEE trial, the "ET" component of the intervention and comparator arm represents AI.
P-value is obtained from the one-sided log-rank test stratified by premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III,
prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world.
Hazard ratio (95% CI) is obtained by Cox PH model stratified by premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III,
prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; RFS: recurrence-free survival.
Source: Novartis Data on File (2024).[2]

Distant disease-free survival (DDFS)

The DDFS results for the comparison of ribociclib plus AI versus AI in Population 5 (NATALEE high-risk ineligible for abemaciclib), derived directly from the NATALEE trial, are presented in Table 7, and the corresponding Kaplan-Meier curve is presented in Figure 7.

Table 7: Summary of DDFS in Population 5 (NATALEE high-risk ineligible for abemaciclib [April 2024 data cut]) from NATALEE

	Ribociclib plus AI (N=891)	AI (N=903)
Number of events, n (%)	[redacted]	[redacted]
p-value log-rank[a]	[redacted]	
HR[b] (95% CI)	[redacted]	

Footnotes: [a] 1-sided p-value for log-rank test stratified by premenopausal women and men vs postmenopausal women, anatomic stage group II vs anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs no) and North America/Western Europe/Oceania vs rest of world.
[b] Hazard rate in group AI + ribociclib versus hazard rate in group AI only is computed using the Cox proportional hazards model with treatment as a single covariate and premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world as stratification factors.
The group ET only is the reference in the hazard ratio calculation.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; DDFS: distant disease-free survival; HR: hazard ratio.
Source: Novartis Data on File (2024).[2]

Figure 7: Kaplan-Meier plot for DDFS in Population 5 (NATALEE high-risk ineligible for abemaciclib [April 2024 data cut]) from NATALEE

Footnotes: As only AI therapies were received in the NATALEE trial, the "ET" component of the intervention and comparator arm represents AI.
P-value is obtained from the one-sided log-rank test stratified by premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III,
prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world.
Hazard ratio (95% CI) is obtained by Cox PH model stratified by premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III,
prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; DDFS: distant disease-free survival ET: endocrine therapy; HR: hazard ratio.
Source: Novartis Data on File (2024).[2]

Overall survival (OS)

The OS results for the comparison of ribociclib plus AI versus AI in Population 5 (NATALEE high-risk ineligible for abemaciclib), derived directly from the NATALEE trial, are presented in Table 8, and the corresponding Kaplan-Meier curve is presented in Figure 8.

Table 8: Summary of OS in Population 5 (NATALEE high-risk ineligible for abemaciclib [April 2024 data cut]) from NATALEE

	Ribociclib plus AI (N=891)	AI (N=903)
Number of events, n (%)	[redacted]	[redacted]
p-value log-rank[a]	[redacted]	
HR[b] (95% CI)	[redacted]	

Footnotes: [a] 1-sided p-value for log-rank test stratified by premenopausal women and men vs postmenopausal women, anatomic stage group II vs anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs no) and North America/Western Europe/Oceania vs rest of world.
[b] Hazard rate in group AI + ribociclib versus hazard rate in group AI only is computed using the Cox proportional hazards model with treatment as a single covariate and premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world as stratification factors.
The group ET only is the reference in the hazard ratio calculation.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; HR: hazard ratio; OS: overall survival.
Source: Novartis Data on File (2024).[2]

Figure 8: Kaplan-Meier plot for OS in Population 5 (NATALEE high-risk ineligible for abemaciclib [April 2024 data cut]) from NATALEE

Footnotes: As only AI therapies were received in the NATALEE trial, the "ET" component of the intervention and comparator arm represents AI.
P-value is obtained from the one-sided log-rank test stratified by premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III,
prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world.
Hazard ratio (95% CI) is obtained by Cox PH model stratified by premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III,
prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; OS: overall survival.
Source: Novartis Data on File (2024).[2]

- **abemaciclib + AI ineligible population with high-risk node-positive disease** (NATALEE trial Population 2 excluding Population 4 [population evaluated in TA810])

Baseline characteristics

The “abemaciclib + AI ineligible population with high-risk node-positive disease (NATALEE trial Population 2 excluding Population 4 [population evaluated in TA810])” referred to by the EAG in this question is herein referred to by the Company as Population 6 (NATALEE node-positive high-risk ineligible for abemaciclib). The baseline characteristics for Population 6 (NATALEE node-positive high-risk ineligible for abemaciclib) can be found in the reference pack accompanying this response, in the zipped folder titled “Population 6 Additional Resources”.

Invasive disease-free survival (iDFS)

The iDFS results for the comparison of ribociclib plus AI versus AI in Population 6 (NATALEE node-positive high-risk ineligible for abemaciclib), derived directly from the NATALEE trial, are presented in Table 9, and the corresponding Kaplan-Meier curve is presented in Figure 9.

Table 9: Summary of iDFS in Population 6 (NATALEE node-positive high-risk ineligible for abemaciclib [April 2024 data cut]) from NATALEE

	Ribociclib plus AI (N=603)	AI (N=570)
Number of events, n (%)	[redacted]	[redacted]
p-value log-rank[a]	[redacted]	
HR[b] (95% CI)	[redacted]	

Footnotes: [a] 1-sided p-value for log-rank test stratified by premenopausal women and men vs postmenopausal women, anatomic stage group II vs anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs no) and North America/Western Europe/Oceania vs rest of world.
[b] Hazard rate in group AI + ribociclib versus hazard rate in group AI only is computed using the Cox proportional hazards model with treatment as a single covariate and premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world as stratification factors.
The group ET only is the reference in the hazard ratio calculation.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; HR: hazard ratio; iDFS: invasive disease-free survival.
Source: Novartis Data on File (2024).[2]

Figure 9: Kaplan-Meier plot for iDFS in Population 6 (NATALEE node-positive high-risk ineligible for abemaciclib [April 2024 data cut]) from NATALEE

Footnotes: As only AI therapies were received in the NATALEE trial, the "ET" component of the intervention and comparator arm represents AI.
P-value is obtained from the one-sided log-rank test stratified by premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world.
Hazard ratio (95% CI) is obtained by Cox PH model stratified by premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; iDFS: invasive disease-free survival; ET: endocrine therapy; HR: hazard ratio.
Source: Novartis Data on File (2024).[2]

Recurrence-free survival (RFS)

The RFS results for the comparison of ribociclib plus AI versus AI in Population 6 (NATALEE node-positive high-risk ineligible for abemaciclib), derived directly from the NATALEE trial, are presented in Table 10, and the corresponding Kaplan-Meier curve is presented in Figure 10.

Table 10: Summary of RFS in Population 6 (NATALEE node-positive high-risk ineligible for abemaciclib [April 2024 data cut]) from NATALEE

	Ribociclib plus AI (N=603)	AI (N=570)
Number of events, n (%)	[redacted]	[redacted]
p-value log-rank[a]	[redacted]	
HR[b] (95% CI)	[redacted]	

Footnotes: [a] 1-sided p-value for log-rank test stratified by premenopausal women and men vs postmenopausal women, anatomic stage group II vs anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs no) and North America/Western Europe/Oceania vs rest of world.
[b] Hazard rate in group AI + ribociclib versus hazard rate in group AI only is computed using the Cox proportional hazards model with treatment as a single covariate and premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world as stratification factors.
The group ET only is the reference in the hazard ratio calculation.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; HR: hazard ratio; RFS: recurrence-free survival.
Source: Novartis Data on File (2024).[2]

Figure 10: Kaplan-Meier plot for RFS in Population 6 (NATALEE node-positive high-risk ineligible for abemaciclib [April 2024 data cut]) from NATALEE

Footnotes: As only AI therapies were received in the NATALEE trial, the "ET" component of the intervention and comparator arm represents AI.
P-value is obtained from the one-sided log-rank test stratified by premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III,
prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world.
Hazard ratio (95% CI) is obtained by Cox PH model stratified by premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III,
prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; RFS: recurrence-free survival.
Source: Novartis Data on File (2024).[2]

Distant disease-free survival (DDFS)

The DDFS results for the comparison of ribociclib plus AI versus AI in Population 6 (NATALEE node-positive high-risk ineligible for abemaciclib), derived directly from the NATALEE trial, are presented in Table 11, and the corresponding Kaplan-Meier curve is presented in Figure 11.

Table 11: Summary of DDFS in Population 6 (NATALEE node-positive high-risk ineligible for abemaciclib [April 2024 data cut]) from NATALEE

	Ribociclib plus AI (N=603)	AI (N=570)
Number of events, n (%)	[redacted]	[redacted]
p-value log-rank[a]	[redacted]	
HR[b] (95% CI)	[redacted]	

Footnotes: [a] 1-sided p-value for log-rank test stratified by premenopausal women and men vs postmenopausal women, anatomic stage group II vs anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs no) and North America/Western Europe/Oceania vs rest of world.
[b] Hazard rate in group AI + ribociclib versus hazard rate in group AI only is computed using the Cox proportional hazards model with treatment as a single covariate and premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world as stratification factors.
The group ET only is the reference in the hazard ratio calculation.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; DDFS: distant disease-free survival; HR: hazard ratio.
Source: Novartis Data on File (2024).[2]

Figure 11: Kaplan-Meier plot for DDFS in Population 6 (NATALEE node-positive high-risk ineligible for abemaciclib [April 2024 data cut]) from NATALEE

Footnotes: As only AI therapies were received in the NATALEE trial, the "ET" component of the intervention and comparator arm represents AI.
P-value is obtained from the one-sided log-rank test stratified by premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III,
prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world.
Hazard ratio (95% CI) is obtained by Cox PH model stratified by premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III,
prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; DDFS: distant disease-free survival; ET: endocrine therapy; HR: hazard ratio.
Source: Novartis Data on File (2024).[2]

Overall survival (OS)

The OS results for the comparison of ribociclib plus AI versus AI in Population 6 (NATALEE node-positive high-risk ineligible for abemaciclib), derived directly from the NATALEE trial, are presented in Table 12, and the corresponding Kaplan-Meier curve is presented in Figure 12.

Table 12: Summary of OS in Population 6 (NATALEE node-positive high-risk ineligible for abemaciclib [April 2024 data cut]) from NATALEE

	Ribociclib plus AI (N=603)	AI (N=570)
Number of events, n (%)	[redacted]	[redacted]
p-value log-rank[a]	[redacted]	
HR[b] (95% CI)	[redacted]	

Footnotes: [a] 1-sided p-value for log-rank test stratified by premenopausal women and men vs postmenopausal women, anatomic stage group II vs anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs no) and North America/Western Europe/Oceania vs rest of world.
[b] Hazard rate in group AI + ribociclib versus hazard rate in group AI only is computed using the Cox proportional hazards model with treatment as a single covariate and premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world as stratification factors.
The group ET only is the reference in the hazard ratio calculation.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; HR: hazard ratio; OS: overall survival.
Source: Novartis Data on File (2024).[2]

Figure 12: Kaplan-Meier plot for OS in Population 6 (NATALEE node-positive high-risk ineligible for abemaciclib [April 2024 data cut]) from NATALEE

Footnotes: As only AI therapies were received in the NATALEE trial, the "ET" component of the intervention and comparator arm represents AI.
P-value is obtained from the one-sided log-rank test stratified by premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world.
Hazard ratio (95% CI) is obtained by Cox PH model stratified by premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world.
Abbreviations: AI: aromatase inhibitor; CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; OS: overall survival.
Source: Novartis Data on File (2024).[2]

A3. Please provide baseline characteristics (including disease characteristics) for NATALEE trial Population 3 (high-risk node-negative disease).

The baseline characteristics and disease characteristics for Population 3 (NATALEE node-negative high-risk) can be found in the reference pack accompanying this, in the zipped folder titled "NATALEE Population 3 Additional Resources".

A4. In Section 2.3.2 of the CS (p49), it is stated that in the NATALEE trial, "patients were allowed to initiate adjuvant ET up to 12 months before enrolling in the trial". However, it is later stated (CS, p49) that "The median duration of prior ET was 2.8 months (min to max: 0 to 16) in the ribociclib plus AI arm and 2.9 months (range: 0 to 54) in the AI arm". Please clarify why the maximum duration of prior ET is greater than 12 months.

The Company acknowledge that [redacted] in the NATALEE trial were recorded to have initiated prior ET more than 12 months before the date of randomisation and therefore contribute to the high maximum durations of prior ET quoted above. A list of these [redacted] and details of their prior ET receipt is presented in [redacted], with further information provided below:

- [redacted] had goserelin for more than 12 months prior to randomisation, permitted as per the NATALEE protocol, which stated that “ovarian suppression is not considered neo-/adjuvant ET”.
- [redacted] were since confirmed to have initiated ET less than 12 months prior to randomisation but were initially counted as having a prior ET agent more than 12 months before the date of randomisation due to a start/end date entry error.
- [redacted] with a prior ET duration of [redacted] months was randomised to the control arm but never treated.
- [redacted] had a prior ET duration of [redacted] at the time of interim analysis 3 (IA3). [redacted] The prior ET from that time was inadvertently included in this analysis. Of note, [redacted] within the 12 months preceding the randomisation to this study.
- [redacted] received prior ET for [redacted] and [redacted] months. These cases were discovered retrospectively after patients were enrolled and the sites were retrained to clarify the trial inclusion criteria requirements. Protocol deviations against Inclusion Criteria 12 (patient may have already received any standard neo-/adjuvant ET at the time of patient informed consent form signature, but randomisation should occur within 12 months of the initial start date of ET. Ovarian suppression or short-term ET for fertility preservation is not considered neo-/adjuvant ET. If patient was receiving tamoxifen as adjuvant ET, a washout period of 5 half-lives [i.e. 35 days] prior to randomisation is required [during that period patient can take AI]) have been applied for all [redacted].

In summary, [redacted] in the NATALEE trial were reported to have initiated prior ET more than 12 months before the date of randomisation. Of these, [redacted] were subsequently identified as misclassifications or did not ultimately receive treatment as part of the NATALEE trial. The remaining [redacted] did receive ET for more than 12 months before the date of randomisation; however, the maximum length of time between ET initiation and randomisation among these [redacted] was [redacted].

Considering the small number of patients ([redacted]) that received prior ET for more than 12 months prior to randomisation and the relatively short duration by which these patients surpassed the 12-month criterion cut-off for ET, the Company concludes that these deviations are likely to have a minimal impact on the interpretation of results for patients who received prior ET in the NATALEE trial.

[redacted] 13 [redacted]

Patient	Arm	Prior ET	Start date	End date	Randomisation date	Duration of ET
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Patient	Arm	Prior ET	Start date	End date	Randomisation date	Duration of ET
[redacted]						

Footnotes: [redacted]

Abbreviations: AI: aromatase inhibitor; ET: endocrine therapy.

Indirect treatment comparison

A5. Please explain the meaning of the footnote to CS, Table 32, i.e., 'The AI arm of the NATALEE trial was used to inform the efficacy of ET'.

Table 32 in the CS refers to the baseline characteristics of the patients included within the MAIC conducted between ribociclib plus AI, abemaciclib plus ET and ET in Population 4B (weighted node-positive high-risk eligible for abemaciclib).

In the MAIC, the control arm of the NATALEE trial was used to inform the efficacy of the comparator ET. The therapies received in the control arm of the NATALEE trial were AIs only (i.e., letrozole and anastrozole); tamoxifen was not received by any patients in the trial. Therefore, the control arm i.e. the AI arm of NATALEE, was used to inform the efficacy of the comparator ET in the MAIC.

As highlighted within the CS, there is a wealth of evidence demonstrating that AIs are more effective than tamoxifen at reducing disease recurrence in EBC. Therefore, using the AI arm of NATALEE to inform the efficacy of the comparator ET in the MAIC can be considered a conservative approach. This was adjusted for within the cost-effectiveness analysis, as described in Section B.3.3.2 of the CS.

A6. Priority question. Please clarify if the method used to estimate comparative efficacy between ribociclib + AI versus ET using NATALEE trial data is based on matching the NATALEE trial ribociclib + AI arm to the monarchE abemaciclib + ET arm and the NATALEE trial AI arm to the monarchE ET arm, respectively, prior to

the calculation of a MAIC HR using weighted data for the NATALEE trial ribociclib + AI and AI arms.

To estimate the comparative efficacy between ribociclib plus AI versus ET in Population 4B (weighted node-positive high-risk eligible for abemaciclib), patients in the ribociclib plus AI and AI arms of the NATALEE trial were selected as per the population included in the monarchE trial Cohort 1. The baseline characteristics of the patients in both arms were then weighted to match the abemaciclib plus ET and ET arms of monarchE Cohort 1 via the MAIC approach to derive weighted Kaplan-Meier curves and corresponding hazard ratios (HRs) to estimate the comparative efficacy between the two arms. Please refer to CS Document B, Section B.2.8.3–2.8.4, and further details of the ITC methodology are presented in the submission appendices in Section D.7.

A7. Please provide details of the digitisation software and processes used to reconstruct iDFS and OS individual patient data from the abemaciclib + ET Kaplan-Meier curves (CS, p102 and p104) and please comment on the accuracy of the recreated Kaplan-Meier curves (CS, Figure 25 and Figure 27) versus the published curves.

Kaplan-Meier curves for abemaciclib plus ET were digitised using a web-based tool, WebPlotDigitizer,[3] and pseudo-individual patient-level data were derived using the published algorithm described by Guyot and colleagues.[4] The recreated Kaplan-Meier curves were subsequently visually inspected to confirm their accuracy in relation to the published curves.

A8. Please provide details of how the monarchE trial missing baseline characteristic values were handled when matching NATALEE-selected data to the monarchE trial population.

Within the MAIC, for categorical baseline characteristics from monarchE with 'missing' as one of the categories, the 'missing' category was adjusted for as long as a non-zero proportion of NATALEE patients had 'missing' for that characteristic. For example, with the Ki-67 characteristic index, patients were index <20, index ≥20, or missing. As such, the NATALEE Population 4A was adjusted to match the proportions with index <20 and index ≥20 in monarchE. Consequently, the proportion with missing Ki-67 in NATALEE also matched to MonarchE; by adjusting on the other two categories (<20 and ≥20), the proportion with missing was also adjusted since the categories are mutually exclusive.

In instances with a 'missing' baseline characteristic in monarchE, but with no patients in NATALEE had 'missing' for that characteristic, the patients with a 'missing' baseline characteristic were omitted and the distribution of the baseline characteristic was re-weighted across the non-missing categories in monarchE.

A9. Priority question. The company states that "Given that the ESS was still relatively large after weighting, use of the MAIC … was considered appropriate" (CS,

p94). However, there is an estimated reduction of [redacted]% and [redacted]% of the selected sample size of the NATALEE trial ribociclib + AI and AI arms, respectively.

As an alternative approach to ITC, please perform STCs for iDFS, DDFS and OS to estimate the comparative efficacy of ribociclib + AI versus abemaciclib + ET, using all patient baseline characteristics included in the primary analysis, and provide the associated programming code as a separate file.

The Company maintains that the MAIC approach was appropriate as the patient numbers in the NATALEE selected, weighted population (Population 4B [weighted node-positive high-risk eligible for abemaciclib]) (ESS=[redacted] and ESS=[redacted] for the ribociclib plus AI and ET arms, respectively) were in line with the suggested reasonable reductions of [redacted]% and [redacted]% in the NICE Decision Support Unit Technical Support Document (TSD) guidance on MAIC/STC (TSD18),[5] and therefore considered high enough for an unanchored MAIC to be robustly performed. TSD18 also notes an average reduction of 80% in ESS across identified population-adjusted ITCs and, in NICE's own worked example of MAIC and STC, the ESS after a reduction in sample size of 63% was described as "still reasonably large".[5] The Company therefore consider that the MAIC approach for the ITC was appropriate to estimate the comparative efficacy of ribociclib plus AI and abemaciclib plus ET, however, have conducted the STC as requested.

Details of the STC methodology and results for iDFS, OS and distant recurrence-free survival (DRFS) between ribociclib plus AI and abemaciclib plus ET in Population 4A (unweighted node-positive high-risk eligible for abemaciclib) are presented below. Notably, while the Company acknowledge the EAG's request for distant disease-free survival (DDFS) results, in the absence of DDFS data for monarchE (the pivotal trial for abemaciclib plus ET in this indication),[6] the Company have conducted the analysis on DRFS, as a close proxy for DDFS. For clarity and to highlight the similarities of the two outcomes, the definitions of both DDFS and DRFS are as follows:

- DDFS, defined by the STEEP criteria,[7] as the time from date of randomisation to date of first event of distant recurrence, death (any cause), or second primary non-breast invasive cancer (excluding basal and squamous cell carcinomas of the skin)
- DRFS, defined as the time from randomisation to distant recurrence or death from any cause

STC methodology

Accelerated failure time (AFT) regression models were used to estimate the effects of differences in baseline characteristics between NATALEE and monarchE on iDFS, OS and DRFS. The analyses were performed independently by treatment arm. Adjustment factors were based on Weibull distributions that were run on patient-level failure time data for iDFS, OS and DRFS from NATALEE. The AFT model included covariates for potentially prognostic characteristics measured at baseline, which were also included in the MAIC presented with the submission. The AFT model included the following covariates:

- Anatomic stage
- Pathological diagnosis term
- Histopathological grade
- Oestrogen receptor/progesterone receptor status

- Tumour size
- Ki67 score at initial diagnosis
- Menopausal status
- Age (years)
- Weight (kg)
- Body mass index (BMI; kg/m²)
- Chemo history
- Eastern Cooperativity Oncology Group performance status
- Prior radiation
- Tumour location
- Race
- Ethnicity
- Region

The model produced a vector of estimated parameters: β. Population means were computed for the baseline characteristics in NATALEE; X_N, and taken from the published aggregate data for monarchE; X_M. A vector of differences between mean values for NATALEE and monarchE were computed as $X_{DNM} = X_N - X_M$. An adjustment factor, $e^{-\psi}$, was computer where $\psi = \sum \beta * X_{DNM}$.

The adjustment factors were applied to the iDFS, OS and DRFS time to events data as: $T_{ADJ\,(i)} = T_{(i)} \times e^{-\psi}$, where $T_{(i)}$ is the unadjusted iDFS, OS or DRFS time for patient (i), and $T_{ADJ(i)}$ is the adjusted iDFS, OS or DRFS time for patient (i), and $e^{-\psi}$ is the adjustment factor for the treatment arm.

Cox proportional hazards regression was then used to derive HRs for iDFS, OS and DRFS. Ribociclib plus AI (from NATALEE Population 4A [unweighted node-positive high-risk eligible for abemaciclib]) was then compared after adjustment to abemaciclib plus AI in monarchE, the latter of which was based on digitised pseudo failure time data from the monarchE trial.[8]

The associated programming code is shared in the reference pack accompanying this response.[9]

STC results

Figure 13 presents the iDFS results for ribociclib plus AI vs abemaciclib plus ET in Population 4A [unweighted node-positive high-risk eligible for abemaciclib]), both unadjusted and adjusted to the monarchE patient characteristics, using the STC method. The estimated HRs for this comparison are presented in Table 14. The estimated HRs are consistent with those estimated from the MAIC for iDFS, suggesting that the results are robust to different population-adjustment methods.

Figure 13: iDFS Kaplan Meier curves, ribociclib plus AI (NATALEE) vs abemaciclib plus ET, unadjusted vs adjusted to monarchE via STC methodology

Footnotes: As only AI therapies were received in the NATALEE trial, the "ET" component of the intervention and comparator arm represents AI.
Abbreviations: AI: aromatase inhibitor; iDFS: invasive disease-free survival; ET: endocrine therapy.

Table 14: iDFS HRs, ribociclib plus AI (NATALEE) vs abemaciclib plus ET, unadjusted vs adjusted to monarchE patient characteristics

Analysis	HR (95% CI)	Estimate	p-value
Ribociclib plus AI vs abemaciclib plus ET (unadjusted)	[redacted]	[redacted]	[redacted]
Ribociclib plus AI vs abemaciclib plus ET (adjusted)	[redacted]	[redacted]	[redacted]

Abbreviations: AI: aromatase inhibitor; CI: confidence interval; iDFS: invasive disease-free survival; ET: endocrine therapy; HR: hazard ratio.

Figure 14 presents the OS results for ribociclib plus AI vs abemaciclib plus ET in Population 4A [unweighted node-positive high-risk eligible for abemaciclib]), both unadjusted and adjusted to the monarchE patient characteristics, using the STC method. The estimated HRs for this comparison are presented in Table 15. As for iDFS, the OS HRs estimated from the STC approach are consistent with those estimated from the MAIC, further suggesting that the results are robust to different population-adjustment methods.

Figure 14: OS Kaplan Meier curves, ribociclib plus AI (NATALEE) vs abemaciclib plus ET, unadjusted vs adjusted to monarchE via STC methodology

Footnotes: As only AI therapies were received in the NATALEE trial, the "ET" component of the intervention and comparator arm represents AI.
Abbreviations: AI: aromatase inhibitor; ET: endocrine therapy; OS: overall survival.

Table 15: OS HRs, ribociclib plus AI (NATALEE) vs abemaciclib plus ET, unadjusted vs adjusted to monarchE patient characteristics

Analysis	HR (95% CI)	Estimate	p-value
Ribociclib plus AI vs abemaciclib plus ET (unadjusted)	[redacted]	[redacted]	[redacted]
Ribociclib plus AI vs abemaciclib plus ET (adjusted)	[redacted]	[redacted]	[redacted]

Abbreviations: AI: aromatase inhibitor; CI: confidence interval; ET: endocrine therapy; HR: hazard ratio; OS: overall survival.

Figure 15 presents the DRFS results for ribociclib plus AI vs abemaciclib plus ET in Population 4A [unweighted node-positive high-risk eligible for abemaciclib]), both unadjusted and adjusted to the monarchE patient characteristics, using the STC method. The estimated HRs for this comparison are presented in Table 16 and are consistent with those estimated for iDFS.

Figure 15: DRFS Kaplan Meier curves, ribociclib plus AI (NATALEE) vs abemaciclib plus ET, unadjusted vs adjusted to monarchE via STC methodology

Footnotes: As only AI therapies were received in the NATALEE trial, the "ET" component of the intervention and comparator arm represents AI.
Abbreviations: AI: aromatase inhibitor; DRFS: distant recurrence-free survival; ET: endocrine therapy.

Table 16: DRFS HRs, ribociclib plus AI (NATALEE) vs abemaciclib plus ET, unadjusted vs adjusted to monarchE patient characteristics

Analysis	HR (95% CI)	Estimate	p-value
Ribociclib plus AI vs abemaciclib plus ET (unadjusted)	[redacted]	[redacted]	[redacted]
Ribociclib plus AI vs abemaciclib plus ET (adjusted)	[redacted]	[redacted]	[redacted]

Abbreviations: AI: aromatase inhibitor; CI: confidence interval; ET: endocrine therapy; DRFS: distant recurrence-free survival; HR: hazard ratio.

A10. Priority question. When assessing proportional hazards, the company explored the Schoenfeld residuals of unweighted and weighted OS for ribociclib+AI versus abemaciclib+ET and states that "the proportional hazards assumption is violated" (CS, Appendix D, p183).

- Please justify the use of a constant HR as a measure of comparative efficacy
- As a sensitivity analysis, please perform ITCs to estimate comparative efficacy using time-varying HRs for iDFS, DDFS and OS, using all patient baseline characteristics included in the primary analysis. Please also provide

a summary of the methodology used to generate the time-varying HRs as well as the associated programming code as a separate file.

While investigating this question, the Company identified that the tests for the proportional hazards (PH) assumption and written interpretation of the results presented in the CS are incorrect (see CS, Appendix D.7.2). The Company can confirm that the PH assumption was not violated for iDFS nor OS in the primary MAIC analysis. The corrected results from the PH testing are presented below.

As described in Appendix D.7.1 of the CS, the validity of the PH assumption between ribociclib plus ET and abemaciclib plus ET, before and after weighting, was tested by a visual inspection of the log-cumulative hazard plots, as well as the Schoenfeld global test of proportionality. The slope of the scaled Schoenfeld residuals was tested using linear regression at an alpha of 0.05; a p-value less than 0.05 indicates that the PH assumption may be violated.

iDFS

As shown in Figure 16, the p-value for the test of Schoenfeld residuals of unweighted iDFS for ribociclib plus ET versus abemaciclib plus ET was not statistically significant (p=[redacted]); the p-value of Schoenfeld residuals for the weighted iDFS with ribociclib plus ET versus abemaciclib plus ET was also not statistically significant (p=[redacted]), suggesting that the PH assumption was not violated.

Figure 16: Updated primary MAIC analysis: proportional hazards assumption test for iDFS based on Schoenfeld residuals (Population 4 [node-positive high-risk eligible for abemaciclib])

A. Unweighted (Population 4A [unweighted node-positive high-risk eligible for abemaciclib])

B. Weighted (Population 4B [weighted node-positive high-risk eligible for abemaciclib])

Abbreviations: iDFS: invasive disease-free survival; MAIC: matching adjusted indirect comparison.

OS

As shown in Figure 17, the p-value for the test of Schoenfeld residuals of unweighted and weighted OS for ribociclib plus ET versus abemaciclib plus ET were both not statistically significant (p=[redacted] and p=[redacted], respectively), suggesting that the PH assumption is also not violated.

Figure 17: Updated proportional hazards assumption test for OS based on Schoenfeld residuals in the primary MAIC analysis (Population 4 [node-positive high-risk eligible for abemaciclib])

A. **Unweighted (Population 4A [unweighted node-positive high-risk eligible for abemaciclib])**

B. **Weighted (Population 4B [weighted node-positive high-risk eligible for abemaciclib])**

Abbreviations: MAIC: matching adjusted indirect comparison; OS: overall survival.

Time-varying HRs

As described above, the corrected results for the PH assumption tests indicate the PH assumption is not violated, meaning a constant HR is appropriate to measure the comparative efficacy between ribociclib plus AI and abemaciclib plus ET. Nevertheless, as requested by the EAG, the Company has conducted additional analyses to estimate results using time-varying HRs for the comparison of iDFS between ribociclib plus AI and abemaciclib plus ET in Population 4B (weighted node-positive high-risk eligible for abemaciclib). Given the PH assumption was not violated, the Company has not conducted the same analyses for DDFS and OS.

To calculate the time-varying HRs, a covariate was added to the Cox proportional hazards model used to estimate the MAIC HR in the primary MAIC analysis for the interaction of treatment effect and time (months). This assumed a linear relationship with time and treatment effect. The associated programming code is shared in the reference pack accompanying this response.[10]

Results for the comparison of iDFS between ribociclib plus AI and abemaciclib plus ET using a continuous time-varying HR are summarised in Table 17. The estimated effect on the HR for ribociclib plus AI versus abemaciclib plus ET for iDFS was [redacted] (95% CI: [redacted]), which was not statistically significant. This suggests the HR for ribociclib plus AI versus abemaciclib plus ET for iDFS in Population 4B (weighted node-positive high-risk eligible for abemaciclib) does not change with time. This finding is consistent with the assessment of the PH assumption for iDFS, which was valid based on test of Schoenfeld residuals.

Table 17: Comparison of iDFS between ribociclib plus AI and abemaciclib plus ET using a continuous time-varying HR (Population 4B [weighted node-positive high-risk eligible for abemaciclib])

iDFS	Estimate (SE)	HR (95% CI)
Treatment effect (ribociclib vs. abemaciclib)	[redacted]	[redacted]
Treatment effect * time (months)	[redacted]	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; SE: standard error.

Section B: Clarification on cost effectiveness data

Updated Company base case economic analyses

Following the receipt of these CQs, the Company have made the following changes to the base case economic analyses:

1. Updated the utility values across on- and off-treatment (see response to CQ B3)
2. Updated the CDK4/6 inhibitor subsequent treatment distribution (see response to CQ B4)
3. Updated the iDFS event distributions (see response to CQ B8)
4. Updated the wastage assumptions for CDK4/6 inhibitors (see response to CQ B9)
5. Updated the RDI for adjuvant abemaciclib (as part of abemaciclib plus ET) (applicable to Population 4A and Population 4B only; see response to CQ B9)

Updated cost-effectiveness results for all Populations are presented in the Appendix to this response.

B1. Priority question. Please provide cost effectiveness results for the following populations:

- **abemaciclib eligible population** (direct evidence: ribociclib + AI versus AI): i.e., NATALEE trial Population 4 (population evaluated in TA810)
- **abemaciclib ineligible population** (direct evidence: ribociclib+AI versus AI)**:** i.e., NATALEE trial Population 1 excluding NATALEE trial Population 4 (population evaluated in TA810).

Updated cost-effectiveness results for Population 4A (unweighted node-positive high-risk eligible for abemaciclib) are presented in the Appendix. Cost effectiveness results for the NATALEE high-risk ineligible for abemaciclib population are not presented as it is the Company's understanding that this population is not used in UK clinical practice and is not a pre-specified subgroup in the NATALEE trial. It should be noted that the Company has provided cost effectiveness results for these patients as part of the Population 1 (NATALEE ITT) base-case analysis which is the focus of this submission and was deemed by clinical experts to be generalisable to UK clinical practice (Appendix Q.3 of the company CS). Baseline characteristics and efficacy data for the NATALEE high-risk ineligible for the abemaciclib population from the NATALEE trial are presented in response to Question A2, which shows the efficacy of ribociclib + AI versus ET in this population is aligned with that of the broader ITT population.

B2. What proportions of NATALEE trial Population 1 and Population 4 patients would receive tamoxifen if treated in NHS practice? Please explain.

As per Page 179 of the CS, the proportion of patients in Population 1 (NATALEE ITT) and Population 4B (weighted node-positive high-risk eligible for abemaciclib) expected to receive tamoxifen if treated within NHS practice were estimated based on feedback from UK clinical experts at an advisory board in September 2024, due to the absence of relevant data from the

NATALEE trial.

As per Appendix Q.3 of the CS, the UK clinical experts agreed upon the following proportions:

- Populations 1–3:
  - Ribociclib plus AI: [redacted]
  - ET: [redacted]
- Population 4B (weighted node-positive high-risk eligible for abemaciclib):
  - Ribociclib plus AI: [redacted]
  - ET: [redacted]
  - Abemaciclib plus ET: [redacted]

During the advisory board meeting , Novartis highlighted that for patients receiving ET monotherapy in Population 1 (NATALEE ITT), the estimated tamoxifen usage of 20% could be considered low, given that NG101 recommends tamoxifen for all premenopausal patients.[11] Despite this recommendation, the clinical experts confirmed that the 20% estimate is considered accurate, noting that the NICE breast cancer guidelines are outdated.

B3. Health-related quality of life tends to decline with increasing disease severity and age. Please provide clinical evidence to explain why (see CS, Table 56 and Table 68):

- baseline iDFS off-treatment utility values are worse than on treatment values
- baseline ET-resistant PPS utility values are worse than ET-sensitive PPS values.

The Company sought additional clinical validation from two clinical experts in response to this question relating to the utility values used in the economic analysis.

The baseline iDFS off- and on-treatment utility values, derived from the NATALEE trial (Population 1 [NATALEE ITT]) were presented to two clinical experts. One clinical expert stated that they would expect the utility values to be similar for patients on- and off-treatment. The second clinical expert stated that it would be reasonable in the short term for patients off treatment to have lower utility as these patients had likely discontinued treatment due to a symptomatic adverse event (AE), although in the long term, the utility values would be similar. Based on this feedback, the Company has updated the base case economic analyses for all populations to include updated utility values derived from the NATALEE trial (Population 1 [NATALEE ITT]), regardless of whether they were on or off-treatment.

As previously described in the CS, Section B.3.4.5, Page 173, the utility values derived for ET were chosen as the referent group as ET has a lower AE profile than ribociclib plus AI. Disutilities were then applied to the ribociclib plus AI arm (Populations 1–5) and the abemaciclib plus ET arm (Populations 4A/4B only). The iDFS utility value from the ET arm was therefore applied for both ribociclib plus AI and ET, in both the on-treatment and off-treatment substates. The values used were from regression Model 3, presented previously in Appendix T.1, Table 130 of the CS, and are shown below in Table 18.

Table 18: Results of GEE regression models estimating EQ-5D utility values in Population 1 (NATALEE ITT)

Health state	Coefficient			Least-squared mean		
	Estimate	SE	p-value	Estimate	SE	p-value
Model 3 – QIC=49,701.10 ; QICu=49,644.00						
Intercept	[redacted]	[redacted]	[redacted]			
iDFS, ribociclib plus AI arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
iDFS, ET arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-metastatic recurrence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Distant recurrence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SPM	[redacted]	[redacted]		[redacted]	[redacted]	
Baseline utility	[redacted]	[redacted]	[redacted]			

Abbreviations: AI: aromatase inhibitor; ET: endocrine therapy; GEE: generalised estimating equation; iDFS: invasive disease-free survival; ITT: intention-to-treat; QIC: quasi-likelihood under the independence model criterion; QICu: corrected quasi-likelihood under the independence model criterion; SE: standard error; SPM: secondary primary malignancy.

Updated economic analysis results, which include this amended base case assumption, are presented in the Appendix.

The baseline ET-resistant and ET-sensitive PPS values were also presented to two clinical experts. In this instance, both clinical experts believed it was reasonable that the ET-resistant PPS utility value would be worse than the ET-sensitive PPS utility value given that ET-resistant disease is often more aggressive. This feedback suggests that the PPS utility values incorporated within the economic analyses (which show ET-resistant PPS utility values as worse than ET-sensitive PPS values) are appropriate.

B4. Priority question. The NHS BlueTeq form permits CDK4/6 inhibitor retreatment if a relapse has occurred >12 months since the completion of treatment with an adjuvant CDK4/6 inhibitor. Please justify the following assumptions used in the economic model:

- in the model ribociclib + AI arm (and the model abemaciclib + ET arm), CDK4/6 inhibitor retreatment is not possible for patients in the DR ET-resistant health state. This assumption has a substantial impact on the total incremental costs associated with ribociclib + AI versus ET but it is not consistent with clinical advice to the company (CS, Appendix Q.3, p414)

The CS model did not account for patients who may receive a CDK4/6 inhibitor in the ET-resistant substate due to conflicting clinical opinion (see CS; Appendix Q.3) and the inability to assign a different treatment mix to patients that would be eligible to receive a CDK4/6 inhibitor in the ET-resistant substate. In light of the EAG's question, the Company has added this functionality in the model and has updated the base case economic analysis.

To account for patients who may still be eligible to receive a CDK4/6 inhibitor in the ET-resistant

substate, this substate has now been divided to consider the treatment mix for CDK4/6 inhibitor-sensitive patients (patients who relapse >12 months since completion of treatment with an adjuvant CDK4/6 inhibitor) as well as CDK4/6 inhibitor-resistant patients (patients who relapse <12 months since completion of treatment with an adjuvant CDK4/6 inhibitor).

The treatment mixes for both the CDK4/6 inhibitor-sensitive and CDK4/6 inhibitor-resistant substates (within the ET-resistant substate) are presented in Table 19 and Table 20, respectively.

The treatment mix among the ET-resistant, CDK4/6 inhibitor-resistant substate is equal to that of the ET-resistant substate presented in the CS. As noted in the CS, this treatment mix was based on UK clinical expert feedback received at the Company advisory board held in September 2024 (see CS; Appendix Q.3).

For the ET-resistant CDK4/6 inhibitor-sensitive substate, clinical experts at the September 2024 advisory board were divided on whether they would rechallenge with CDK4/6 inhibitor (see CS; Appendix Q.3). However, all clinical experts agreed that if they were to rechallenge with a CDK4/6 inhibitor they would use a different CDK4/6 inhibitor to the one used in the adjuvant setting. To reflect the conflicting clinical opinion the treatment mix for the ET-resistant, CDK4/6 inhibitor-sensitive substate includes [redacted] total CDK4/6i use (1/3 of the CDK4/6 inhibitor use compared to patients that receive adjuvant ET monotherapy), with 0% ribociclib use if the patient had received adjuvant ribociclib and 0% abemaciclib use if the patient has received adjuvant abemaciclib (Table 20). The remaining treatments in the treatment mix reflect that of the ET-resistant CDK4/6 inhibitor-resistant substate (but reduced to make up the remaining [redacted]).

Table 19: Treatment mix for DR ET-resistant state – CDK4/6 inhibitor-resistant patients

Post-progression treatment	Ribociclib plus AI	ET	Abemaciclib plus ET
Ribociclib plus fulvestrant	[redacted]	[redacted]	[redacted]
Palbociclib plus fulvestrant	[redacted]	[redacted]	[redacted]
Abemaciclib plus fulvestrant	[redacted]	[redacted]	[redacted]
Everolimus plus exemestane	[redacted]	[redacted]	[redacted]
Capecitabine	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
Alpelisib	[redacted]	[redacted]	[redacted]

Abbreviations: AI: aromatase inhibitor; ET: endocrine therapy.

Table 20: Treatment mix for DR ET-sensitive state – CDK4/6 inhibitor-sensitive patients

Post-progression treatment	Ribociclib plus AI	ET	Abemaciclib plus ET
Ribociclib plus fulvestrant	[redacted]	[redacted]	[redacted]
Palbociclib plus fulvestrant	[redacted]	[redacted]	[redacted]
Abemaciclib plus fulvestrant	[redacted]	[redacted]	[redacted]
Everolimus plus exemestane	[redacted]	[redacted]	[redacted]
Capecitabine	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
Alpelisib	[redacted]	[redacted]	[redacted]

Abbreviations: AI: aromatase inhibitor; ET: endocrine therapy.

Updated cost-effectiveness results, which include this amended base case assumption, are presented in the Appendix.

- DR ET-sensitive health state values (CS, Table 59) are not consistent with the values suggested by clinical advice to the company (CS, Appendix Q.3, Table 112).

The Company acknowledges that the feedback of the clinical experts at the September 2024 advisory board implied greater CDK4/6 inhibitor retreatment than what was included in the CS. Although the clinical experts noted the recent update to the NHS Blueteq form to permit CDK4/6 inhibitor retreatment in specific patients, it is unclear how this update will impact prescribing in the metastatic breast cancer setting. As such, the CS adopted a middle value of [redacted] total CDK4/6 inhibitor retreatment to account for the inherent uncertainty around the clinician estimates.

B5. Priority question. Please provide 95% confidence intervals for the proportion of iDFS events that are SPM, NMR, DR or death from the NATALEE trial (CS, Table 46).

As requested, the 95% confidence intervals for the proportion of iDFS events that are SPM, NMR, DR or death from the NATALEE trial are presented in Table 21.

Table 21. Proportion of iDFS events from the NATALEE trial

Analysis/ Treatment arm	Number of events	% iDFS events that are NMR (95% CI)	% iDFS events that are death (95% CI)	% iDFS events that are DR (95% CI)	% iDFS events that are SPM (95% CI)	% iDFS events Missing type (95% CI)
Base case (Population 1 [NATALEE ITT])						
Ribociclib plus AI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Population 2 (NATALEE node-positive high-risk)						
Ribociclib plus AI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Population 3 (NATALEE node-negative high-risk)						
Ribociclib plus AI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Population 4A (unweighted node-positive high-risk eligible for abemaciclib)						
Ribociclib plus AI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Population 4B (weighted node-positive high-risk eligible for abemaciclib)						

Ribociclib plus AI						
ET						

Abbreviations: AI: aromatase inhibitor; CI: confidence interval; DR: distant recurrence; iDFS: invasive disease-free survival; ITT: intent to treat; NMR: non-metastatic recurrence; SPM: secondary primary neoplasm.

B6. In the model, once iDFS treatment waning starts, the distribution of iDFS events for ribociclib + AI patients matches the distribution of iDFS events for ET patients. Please fully justify this approach to treatment waning given that it is stated (CS, p144) that the distribution of iDFS events was assumed to be constant over time.

In the base case economic analysis, the treatment waning process was designed such that the distribution of iDFS events for patients receiving ribociclib plus AI begins to linearly approach the distribution observed for ET patients. This continues until the end of the treatment waning period. This approach mirrors the treatment effect waning where the benefit of ribociclib plus AI relative to ET diminishes over time, ultimately aligning the risk of iDFS events for ribociclib plus AI with that for ET. The Company acknowledge that the description in the CS, stating that the distribution of iDFS events was assumed to be constant over time, does not adequately explain this process.

The current methodology (as described above) ensures consistency in modelling the gradual loss of benefit seen with ribociclib plus AI and aligns the transition probabilities for AI patients with those of ET patients once the treatment effect has fully waned. While the Company maintain that this approach is appropriate, the Company has conducted a scenario analysis where the distribution of iDFS events is assumed to remain constant over time (i.e., the distribution of iDFS events for patients receiving ribociclib plus AI does not change over time to approach the iDFS event distribution of patients receiving ET as per the base case).

Results of this scenario analysis are presented for each population in the Appendix. Notably, the results show that this scenario analysis has minimal impact on the base case results.

B7. The distribution of iDFS events for ET patients (CS, Table 46) for NATALEE trial Population 3 is substantially different overall compared with NATALEE trial Population 2 and Population 4. Please provide clinical justification for these differences.

In response to this CQ and CQ B8 below, the Company sought additional clinical validation from two clinical experts. The points raised and conclusions drawn relating to the iDFS event distributions by treatment arm are provided in response to CQ B8.

B8. The distribution of iDFS events between ribociclib + AI patients and ET patients (CS, Table 46) is substantially different across NATALEE trial Population 2,

Population 3 and Population 4. Please provide clinical justification for these differences.

As noted above, the Company sought additional clinical validation from two clinical experts to address the differences relating to the distribution of iDFS events by treatment arm across Population 2 (NATALEE node-positive high-risk), Population 3 (NATALEE node-negative high-risk), and Population 4B (weighted node-positive high-risk eligible for abemaciclib).

One clinical expert noted that the distribution of iDFS events for Population 4 (i.e. Population 4B [weighted node-positive high-risk eligible for abemaciclib]) has low clinical plausibility as they would expect the proportion of DR events to be lower for patients receiving ribociclib plus AI compared to those receiving ET monotherapy. Both clinical experts also noted that the proportion of patients experiencing death in Population 3 (NATALEE node-negative high-risk) is less plausible as they would expect patients with ribociclib plus AI to have fewer deaths than patients receiving ET monotherapy, although noted these could be non-breast cancer related deaths. Both clinical experts suggested that the variation in results between the populations was likely due to chance and small sample size.

In contrast, both clinical experts indicated that the results for the ITT population (i.e., Population 1 [NATALEE ITT]) were clinically plausible as they would expect patients that receive ribociclib plus AI to have a reduced proportion of DR and NMR events, as per the mechanism of action of ribociclib plus AI. Both clinical experts suggested it would be more appropriate to use the ITT iDFS event distribution for all populations.

Based on this feedback from clinical experts, the Company has amended the base case analysis assumption for the distribution of iDFS events across all populations to reflect the iDFS event distribution reported in Population 1 (NATALEE ITT), given this was determined to be clinically plausible by clinical experts.

The revised base case results, which include this amended base case assumption, are presented in the Appendix.

B9. Please explain in more detail than is currently included in the CS (Table 69) why it is not considered appropriate to include wastage for ribociclib.

Across all four economic analyses, the drug acquisition costs of ribociclib were calculated based on the anticipated licensed dosing regimen and the dosing regimen used in NATALEE.[12, 13] This is 400 mg (two 200 mg film-coated tablets) administered orally once daily for 21 consecutive days followed by seven days off treatment, resulting in a complete treatment cycle of 28 days.

A RDI of [redacted] for ribociclib was also applied, derived from the ITT population of the NATALEE trial (April 2024 data cut]).[14] The cost of ribociclib is priced linearly, such that the cost per mg remains the same between packages of different dose amounts. Cost reductions for permitted dose reductions of ribociclib (from 400 mg to 200 mg in the case of potential toxicities) were therefore assumed to be fully captured in the RDI, which counts these dose reductions as being below the planned dose. Given the pack format, dosing and linear pricing of ribociclib, a down-dosing wastage assumption is not considered relevant for ribociclib. In contrast, as explained on page 180 of the CS, a down-dosing wastage assumption was considered relevant for abemaciclib and included in the CS.

The Company note that it may be appropriate to consider wastage due to reasons other than down-dosing for both ribociclib and abemaciclib and as such, have amended the base case economic analyses across all populations to include a wastage assumption for ribociclib and abemaciclib. Specifically, wastage was accounted for by calculating the average cumulative amount of medication (mg) consumed since treatment initiation and rounding up to the nearest whole package of medication. Average medication (mg) consumed by cycle was calculated as the recommended dose in that cycle multiplied by the corresponding RDI. The cumulative average medication consumed was calculated for each cycle n as the sum of medication consumed in cycles 1 through n. The result was then divided by the pack size (mg per package) and rounded up to the nearest whole number to yield the number of packs required by cycle. Finally, costs of drug acquisition were applied by multiplying the marginal number of packs required since treatment initiation by the pack price, accounting for discounts (if applicable).

The revised cost-effectiveness results, which include this amended base case assumption, are presented in the Appendix. Notably, the results show that the inclusion of this additional wastage assumption has minimal impact on the base case results.

Additionally, while investigating wastage in response to this CQ, the Company identified an error in the methodology used to determine the RDI for ribociclib due to treatment holds, which informs the RDI for adjuvant abemaciclib (as part of abemaciclib plus ET).

The Company now propose to use patient level data from NATALEE directly, which reflects time on treatment holds (i.e. dose interruptions). The Company estimate, using SAP-specified definition of dose interruptions, that mean time on dose holds due to any reason is [redacted] days (median [redacted] days, SD [redacted] days) per patient (n=2,526, safety set). As previously estimated, the mean exposure to ribociclib is [redacted] months.

Using the following formula, the adjustment of time due to treatment holds would be:

[redacted]

The Company apologises for this error and presents the revised calculation for determining RDI due to treatment holds, which equates to an RDI for abemaciclib of [redacted] which will be used in the base case economic analyses for all applicable populations (i.e. Population 4A and Population 4B) going forward.

Section C: Textual clarification and additional points

C1. Please provide the NATALEE trial statistical analysis plan.

The original statistical analysis plan can be found at the end of the NATALEE protocol document, from Page 270; the final statistical analysis plan can be found in this same document, from page 327. This was provided as part of the reference pack to the CS, but has been reshared in the reference pack alongside this response for completeness.

C2. Please provide the MONALEESA-2 and MONALEESA-3 trial CSRs and statistical analysis plans.

The MONALEESA-2 and MONALEESA-3 trial CSRs and statistical analysis plans have been included in the reference pack alongside this response.[15-18]

Please note that a CSR for the latest data cut-off of MONALEESA-3 (January 2022) was not produced by Novartis. The CSR from the previous June 2019 data cut-off has therefore been provided, in addition to the MONALEESA-3 publication that includes the results from the January 2022 data cut-off.[19]

C3. Please clarify whether the search terms provided in CS, Appendix D2, Table 1 were used to search both the Embase® and MEDLINE® databases using Embase.com.

Yes, the search terms provided in Appendix D.2, Table 1 (page 17) were used to search both the Embase® and MEDLINE® databases using Embase.com.

C4. Please confirm whether the number of records screened (CS, Appendix G, Figure 14) in the July 2024 economic evaluation systematic literature review (SLR) was 86.

Yes, the number of records screened in the July 2024 economic evaluation SLR was 86 (Appendix G.4, Figure 15, page 212).

C5. In the CS (Table 56 and Table 68) the base case utility values for iDFS on-treatment versus iDFS off-treatment differ, but are assumed equal in the company model ('Utilities State'!E12:E13). Please confirm which is the correct iDFS off-treatment value.

The Company does not believe there is a discrepancy here. The base case health state utility values for iDFS on-treatment and iDFS off-treatment are not set equal in the Company model. The on-treatment iDFS utility value is [redacted] ('Utilities State'!E12:E13), while the off-treatment iDFS utility value is [redacted] ('Utilities State'!F12:F13), in line with Table 56 of the CS. These utility values are not treatment-dependent; the same iDFS on-treatment and iDFS off-treatment utility values are used for ribociclib plus AI, ET, and abemaciclib plus ET.

C6. The abemaciclib RDI value (CS, Table 58) does not match the value used in the economic model. Please clarify which is the correct value and provide the calculations used to estimate this value.

The Company does not believe there is a discrepancy in the abemaciclib RDI value between the CS and the CS economic model. A value of [redacted] was presented as the RDI in Table 58 of the CS and was also reflected in the CS economic model (load Population 4; 'Regimens Dose'!N27).

C7. Please clarify how many independent reviewers completed the NATALEE trial (CS, Table 14) and the monarchE trial (CS, Appendix D.10, Table 23) quality assessments.

The quality assessments of the NATALEE trial (Document B.2.4.1, Table 14, page 63) and monarchE trial (Appendix D.10, Table 23, page 190) were conducted using the York Centre for Reviews and Dissemination (CRD) checklist.[20] They were conducted first by one reviewer and checked by a second reviewer. Any discrepancies were resolved by a third reviewer.

C8. Please clarify whether the MAIC OS result for ribociclib+AI versus abemaciclib+ET provided on p123 of the CS should be reported as [redacted]

The Company apologises for this oversight. The correct value for the MAIC OS result for ribociclib plus AI versus abemaciclib plus ET in Document B.2.11.1, page 123 should be reported [redacted]), and not [redacted]) as is currently reported.

Appendix

Updated base case results

Population 1 (NATALEE ITT)

Probabilistic base case results for the economic analysis of ribociclib plus AI vs ET in Population 1 (NATALEE ITT) are presented in Table 22.

Table 22: Probabilistic base case results: ribociclib plus AI vs ET – Population 1 (NATALEE ITT)

	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	NHB £20,000 per QALY	NHB £30,000 per QALY
ET	[redacted]	15.01	[redacted]						
Ribociclib plus AI	[redacted]	15.65	[redacted]	[redacted]	0.64	[redacted]	Dominant	0.57	0.54

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; Incr: incremental; ITT: intention to treat; LYG: life years gained; NHB: net health benefit; QALYs: quality-adjusted life years.

A scatter plot showing the incremental costs and QALYs from the 1,000 iterations of the PSA for ribociclib plus AI vs ET in Population 1 (NATALEE ITT) is presented in Figure 18.

Figure 18: PSA scatter plot for ribociclib plus AI vs ET – Population 1 (NATALEE ITT)

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; ITT: intention to treat; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years; WTP: willingness to pay.

Scenario analysis

The results for all scenario analyses conducted in Population 1 (NATALEE ITT) are presented in Table 23.

Table 23: Scenario analysis results – Population 1 (NATALEE ITT)

Parameter	Base case	Scenario analysis	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Base case			[redacted]	[redacted]	**Dominant**	**0.554**	**0.530**
iDFS extrapolation (ribociclib plus AI/ET)	Exponential	Log-logistic (R)	[redacted]	[redacted]	Dominant	0.442	0.436
		Gamma (R)	[redacted]	[redacted]	Dominant	0.591	0.557
HR for efficacy of tamoxifen vs AIs	HR: 1.10 (Liao *et al.* [2022])[21]	HR: 1.45 (Janni *et al.* [2023])[22]	[redacted]	[redacted]	Dominant	0.701	0.660
		HR: 1 (Assumption)	[redacted]	[redacted]	Dominant	0.511	0.492
Treatment waning	'Carryover benefit' of a constant treatment effect lasting up to 8 years, after which the treatment effect was modelled to wane, to the point at which the iDFS event rate was equal to general population mortality	Treatment effect assumed constant, and life-long, with no treatment waning	[redacted]	[redacted]	Dominant	0.735	0.674
		Treatment effect assumed constant up to 10 years	[redacted]	[redacted]	Dominant	0.582	0.555
		Treatment effect assumed constant up to 5 years	[redacted]	[redacted]	Dominant	0.502	0.485
		Treatment effect assumed constant up to 5 years, with treatment waning from Years 5–8 only	[redacted]	[redacted]	5,647	0.182	0.206
Efficacy of post-progression therapies in DR health state	ET-resistant MONALEESA-3 OS: Loglogistic (R)	ET-resistant MONALEESA-3 OS: Weibull (R)	[redacted]	[redacted]	2,903	0.463	0.489
	ET-resistant MONALEESA-3 PFS: Lognormal (R)	ET-resistant MONALEESA-3 PFS: Lognormal (U)	[redacted]	[redacted]	Dominant	0.545	0.524
	ET-resistant MONALEESA-3 TTD: Gompertz (R)	ET-resistant MONALEESA-3 TTD: RCS Weibull (R)	[redacted]	[redacted]	Dominant	0.498	0.493

	ET-sensitive MONALEESA-2 OS: Log-logistic	ET-sensitive MONALEESA-2 OS: Gamma	[redacted]	[redacted]	Dominant	0.600	0.568
	ET-sensitive MONALEESA-2 PFS: Lognormal	ET-sensitive MONALEESA-2 PFS: Exponential	[redacted]	[redacted]	Dominant	0.654	0.599
	ET-sensitive MONALEESA-2 TTD: Exponential	ET-sensitive MONALEESA-2 TTD: Weibull	[redacted]	[redacted]	Dominant	0.573	0.543
	Estimated HRs for PFS, OS and TTD for the given comparator vs ribociclib plus fulvestrant, based on published literature (ET-sensitive substate only): For capecitabine: OS HR: 1.32; PFS HR: 1.64; TTD HR: as per PFS	PFS/OS/TTD HRs for capecitabine were assumed equivalent to letrozole/anastrozole	[redacted]	[redacted]	Dominant	0.572	0.521
Treatment mix of AI/ET (iDFS health state)	Aligned to clinical expert estimates for Population 1 from the September 2024 advisory board (see Appendix Q.3). Estimates for proportion of patients receiving goserelin in addition to ribociclib plus AI adjusted based on literature.	iDFS treatment mix of AI (as part of ribociclib plus AI) and the ET comparator based on those estimated by clinical experts for Population 4	[redacted]	[redacted]	Dominant	0.532	0.511
		Proportion of patients receiving goserelin based on the NATALEE trial (ITT population; April 2024 data cut)	[redacted]	[redacted]	Dominant	0.560	0.534
Treatment mix (DR health state)	45% of patients in the ribociclib plus AI arm of the model would receive retreatment with a CDK4/6 inhibitor in the ET-sensitive DR health state	90% of the ribociclib plus AI arms (and abemaciclib plus ET arm in Population 4) received CDK4/6 rechallenge as per ET arm (ET-sensitive DR health state)	[redacted]	[redacted]	2,033	0.462	0.479
		70% of the ribociclib plus AI arms (and abemaciclib plus ET arm in Population 4) received CDK4/6 rechallenge (ET-sensitive DR health state)	[redacted]	[redacted]	Dominant	0.503	0.502

RDI	RDIs for AI (as part of ribociclib plus AI) and ET (including goserelin) derived from the NATALEE trial	RDIs for all ETs (monotherapy and in combination with a CDK4/6 inhibitor), goserelin and zoledronic acid, were assumed to be [redacted].	[redacted]	[redacted]	Dominant	0.554	0.530
Time on treatment extrapolation (AI [as part of ribociclib plus AI] and ET)	Weibull (R)	Gamma (R)	[redacted]	[redacted]	Dominant	0.554	0.530
Maximum duration of treatment (AI/ET)	5 years	7 years	[redacted]	[redacted]	Dominant	0.604	0.566
		10 years	[redacted]	[redacted]	Dominant	0.667	0.610
Health state utility values	iDFS (on-treatment: 0.7620; off-treatment: 0.7367) and NMR (0.6818) health state utility values derived from EQ-5D-5L data collected directly in NATALEE (ITT population) and mapped onto the EQ-5D-3L UK value set using the mapping function developed by Hernández Alava *et al.* (2017)	iDFS and NMR health state utility values based on those used in TA810 (iDFS: 0.782; NMR: 0.760)	[redacted]	[redacted]	Dominant	0.569	0.545
iDFS event distribution	Distribution of iDFS events for patients receiving ribociclib plus AI begins to linearly approach the distribution observed for ET patients, until the end of the treatment waning period	Distribution of iDFS events is assumed to remain constant over time	[redacted]	[redacted]	Dominant	0.540	0.526

Abbreviations: AE: adverse event; AI: aromatase inhibitor; CDK4/6: cyclin dependent kinase 4/6; DR: distant recurrence; EQ-5D: EuroQoL-5dimensions; ET: endocrine therapy; HR: hazard ratio; iDFS: invasive disease-free survival; ITT: intention-to-treat; MAIC: matching-adjusted indirect comparison; NHB: net health benefit; NICE: National Institute for Health and Care Excellence; NMR: non-metastatic recurrence; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; R: restricted; RCS: restricted cubic spline; RDI: relative dose intensity; TA: technology appraisal; TTD: time-to-treatment discontinuation; U: unrestricted.

Updated subgroup analyses results

Population 2 (NATALEE node-positive high-risk)

Probabilistic subgroup analysis results for the economic analysis of ribociclib plus AI vs ET in Population 2 (NATALEE node-positive high-risk) are presented in Table 24.

Table 24: Probabilistic subgroup analysis results: ribociclib plus AI vs ET – Population 2 (NATALEE node-positive high-risk)

	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	NHB £20,000 per QALY	NHB £30,000 per QALY
ET	[redacted]	14.94	[redacted]						
Ribociclib plus AI	[redacted]	15.58	[redacted]	[redacted]	0.63	[redacted]	Dominant	0.58	0.55

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gained; NHB: net health benefit; QALYs: quality-adjusted life years.

A scatter plot showing the incremental costs and QALYs from the 1,000 iterations of the PSA for ribociclib plus AI vs ET in Population 2 (NATALEE node-positive high-risk) is presented in Figure 19.

Figure 19: PSA scatter plot for ribociclib plus AI vs ET – Population 2 (NATALEE node-positive high-risk)

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years; WTP: willingness to pay.

Scenario analysis

The results for all scenario analyses conducted in Population 2 (NATALEE node-positive high-risk) are presented in Table 25.

Table 25: Scenario analysis results vs ET – Population 2 (NATALEE node-positive high-risk)

Parameter	Base case	Scenario analysis	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Base case			[redacted]	[redacted]	**Dominant**	**0.586**	**0.555**
iDFS extrapolation (ribociclib plus AI/ET)	Exponential	Gamma (U)	[redacted]	[redacted]	Dominant	0.540	0.510
		Weibull (U)	[redacted]	[redacted]	Dominant	0.555	0.522
HR for efficacy of tamoxifen vs AIs	HR: 1.10 (Liao *et al*. [2022])[21]	HR: 1.45 (Janni *et al*. [2023])[22]	[redacted]	[redacted]	Dominant	0.737	0.689
		HR: 1 (Assumption)	[redacted]	[redacted]	Dominant	0.542	0.517
Treatment waning	'Carryover benefit' of a constant treatment effect lasting up to 8 years, after which the treatment effect was modelled to wane, to the point at which the iDFS event rate was equal to general population mortality	Treatment effect assumed constant, and life-long, with no treatment waning	[redacted]	[redacted]	Dominant	0.758	0.693
		Treatment effect assumed constant up to 10 years	[redacted]	[redacted]	Dominant	0.613	0.579
		Treatment effect assumed constant up to 5 years	[redacted]	[redacted]	Dominant	0.535	0.511
		Treatment effect assumed constant up to 5 years, with treatment waning from Years 5–8 only	[redacted]	[redacted]	4,339	0.201	0.220
Efficacy of post-progression therapies in DR health state	ET-resistant MONALEESA-3 OS: Loglogistic(R)	ET-resistant MONALEESA-3 OS: Weibull (R)	[redacted]	[redacted]	2,265	0.492	0.513
	ET-resistant MONALEESA-3 PFS: Lognormal (R)	ET-resistant MONALEESA-3 PFS: Lognormal (U)	[redacted]	[redacted]	Dominant	0.577	0.549
	ET-resistant MONALEESA-3 TTD: Gompertz (R)	ET-resistant MONALEESA-3 TTD: RCS Weibull (R)	[redacted]	[redacted]	Dominant	0.529	0.517

Parameter	Base case	Scenario analysis	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
	ET-sensitive MONALEESA-2 OS: Log-logistic	ET-sensitive MONALEESA-2 OS: Gamma	[redacted]	[redacted]	Dominant	0.632	0.594
	ET-sensitive MONALEESA-2 PFS: Lognormal	ET-sensitive MONALEESA-2 PFS: Exponential	[redacted]	[redacted]	Dominant	0.687	0.625
	ET-sensitive MONALEESA-2 TTD: Exponential	ET-sensitive MONALEESA-2 TTD: Weibull	[redacted]	[redacted]	Dominant	0.605	0.568
	Estimated HRs for PFS, OS and TTD for the given comparator vs ribociclib plus fulvestrant, based on published literature: For capecitabine in ET-sensitive: OS HR: 1.32; PFS HR: 1.64; TTD HR: as per PFS	PFS/OS/TTD HRs for capecitabine were assumed equivalent to letrozole/anastrozole	[redacted]	[redacted]	Dominant	0.605	0.546
Treatment mix of AI/ET (iDFS health state)	Aligned to clinical expert estimates for Population 1 from the September 2024 advisory board (see Appendix Q.3). Estimates for proportion of patients receiving goserelin in addition to ribociclib plus AI adjusted based on literature.	iDFS treatment mix of AI (as part of ribociclib plus AI) and the ET comparator based on those estimated by clinical experts for Population 4	[redacted]	[redacted]	Dominant	0.563	0.536
		Proportion of patients receiving goserelin based on the NATALEE trial (ITT population; April 2024 data cut)	[redacted]	[redacted]	Dominant	0.591	0.559
Treatment mix (DR health state)	45% of patients in the ribociclib plus AI arm of the model would receive retreatment with a CDK4/6 inhibitor in the ET-sensitive DR health state	90% of the ribociclib plus AI arms (and abemaciclib plus ET arm in Population 4) received CDK4/6 rechallenge as per ET arm (ET-sensitive DR health state)	[redacted]	[redacted]	1,305	0.492	0.503
		70% of the ribociclib plus AI arms (and abemaciclib plus ET arm in Population 4) received CDK4/6 rechallenge (ET-sensitive DR health state)	[redacted]	[redacted]	Dominant	0.534	0.526

Parameter	Base case	Scenario analysis	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
RDI	Same RDIs for AI (as part of ribociclib plus AI) and ET were assumed as per Population 1.	RDIs for all ETs (monotherapy and in combination with a CDK4/6 inhibitor), goserelin and zoledronic acid, were assumed to be [redacted].	[redacted]	[redacted]	Dominant	0.586	0.555
Time on treatment extrapolation (AI [as part of ribociclib plus AI] and ET)	Weibull (R)	Loglogistic (R)	[redacted]	[redacted]	Dominant	0.598	0.564
Maximum duration of treatment (AI/ET)	5 years	7 years	[redacted]	[redacted]	Dominant	0.638	0.592
		10 years	[redacted]	[redacted]	Dominant	0.701	0.637
Health state utility values	iDFS (on-treatment: 0.7620; off-treatment: 0.7367) and NMR (0.6818) health state utility values derived from EQ-5D data collected directly in NATALEE (ITT population)	iDFS and NMR health state utility values based on those used in TA810 (iDFS: 0.782; NMR: 0.760)	[redacted]	[redacted]	Dominant	0.599	0.569
iDFS event distribution	Distribution of iDFS events for patients receiving ribociclib plus AI begins to linearly approach the distribution observed for ET patients, until the end of the treatment waning period	Distribution of iDFS events is assumed to remain constant over time	[redacted]	[redacted]	Dominant	0.573	0.552

Abbreviations: AE: adverse event; AI: aromatase inhibitor; CDK4/6: cyclin dependent kinase 4/6; DR: distant recurrence; EQ-5D: EuroQoL-5dimensions; ET: endocrine therapy; HR: hazard ratio; iDFS: invasive disease-free survival; MAIC: matching-adjusted indirect comparison; NHB: net health benefit; NICE: National Institute for Health and Care Excellence; NMR: non-metastatic recurrence; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; R: restricted; RCS: restricted cubic spline; RDI: relative dose intensity; TA: technology appraisal; TTD: time-to-treatment discontinuation; U: unrestricted.

Population 3 (NATALEE node-negative high-risk)

Probabilistic subgroup analysis results for the economic analysis of ribociclib plus AI vs ET in Population 3 (NATALEE node-negative high-risk) are presented in Table 26.

Table 26: Probabilistic subgroup analysis results: ribociclib plus AI vs ET – Population 3 (NATALEE node-negative high-risk)

	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	NHB £20,000 per QALY	NHB £30,000 per QALY
ET	[redacted]	14.94	[redacted]	-	-	-	-	-	-
Ribociclib plus AI	[redacted]	15.43	[redacted]	[redacted]	0.50	[redacted]	4,186	0.30	0.33

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gained; NHB: net health benefit; QALYs: quality-adjusted life years.

A scatter plot showing the incremental costs and QALYs from the 1,000 iterations of the PSA for ribociclib plus AI vs ET in Population 3 (NATALEE node-negative high-risk) is presented in Figure 20.

Figure 20: PSA scatter plot for ribociclib plus AI vs ET – Population 3 (NATALEE node-negative high-risk)

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years; WTP: willingness to pay.

Scenario analysis

The results for all scenario analyses conducted in Population 3 (NATALEE node-negative high-risk) are presented in Table 27.

Table 27: Scenario analysis results vs ET – Population 3 (NATALEE node-negative high-risk)

Parameter	Base case	Scenario analysis	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Base case			[redacted]	[redacted]	**593**	**0.411**	**0.415**
iDFS extrapolation (ribociclib plus AI/ET)	RCS log-logistic (U)	Generalised gamma (U)	[redacted]	[redacted]	8,376	0.204	0.253
		Generalised F (U)	[redacted]	[redacted]	12,215	0.128	0.194
HR for efficacy of tamoxifen vs AIs	HR: 1.10 (Liao *et al.* [2022])[21]	HR: 1.45 (Janni *et al.* [2023])[22]	[redacted]	[redacted]	Dominant	0.544	0.531
		HR: 1 (Assumption)	[redacted]	[redacted]	1,383	0.372	0.381
Treatment waning	'Carryover benefit' of a constant treatment effect lasting up to 8 years, after which the treatment effect was modelled to wane, to the point at which the iDFS event rate was equal to general population mortality	Treatment effect assumed constant, and life-long, with no treatment waning	[redacted]	[redacted]	Dominant	0.509	0.494
		Treatment effect assumed constant up to 10 years	[redacted]	[redacted]	120	0.433	0.434
		Treatment effect assumed constant up to 5 years	[redacted]	[redacted]	1,558	0.365	0.375
		Treatment effect assumed constant up to 5 years, with treatment waning from Years 5–8 only	[redacted]	[redacted]	10,678	0.115	0.159
Efficacy of post-progression therapies in DR health state	ET-resistant MONALEESA-3 OS: Loglogistic(R)	ET-resistant MONALEESA-3 OS: Weibull (R)	[redacted]	[redacted]	5,998	0.334	0.382
	ET-resistant MONALEESA-3 PFS: Lognormal (R)	ET-resistant MONALEESA-3 PFS: Lognormal (U)	[redacted]	[redacted]	925	0.403	0.410
	ET-resistant MONALEESA-3 TTD: Gompertz (R)	ET-resistant MONALEESA-3 TTD: RCS Weibull (R)	[redacted]	[redacted]	2,816	0.364	0.383
	ET-sensitive MONALEESA-2 OS: Log-logistic	ET-sensitive MONALEESA-2 OS: Gamma	[redacted]	[redacted]	Dominant	0.455	0.451

Parameter	Base case	Scenario analysis	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
	ET-sensitive MONALEESA-2 PFS: Lognormal	ET-sensitive MONALEESA-2 PFS: Exponential	[redacted]	[redacted]	Dominant	0.505	0.480
	ET-sensitive MONALEESA-2 TTD: Exponential	ET-sensitive MONALEESA-2 TTD: Weibull	[redacted]	[redacted]	Dominant	0.429	0.427
	Estimated HRs for PFS, OS and TTD for the given comparator vs ribociclib plus fulvestrant, based on published literature: For capecitabine in ET-sensitive: OS HR: 1.32; PFS HR: 1.64; TTD HR: as per PFS	PFS/OS/TTD HRs for capecitabine were assumed equivalent to letrozole/anastrozole	[redacted]	[redacted]	Dominant	0.429	0.406
Treatment mix of AI/ET (iDFS health state)	Aligned to clinical expert estimates for Population 1 from the September 2024 advisory board (see Appendix Q.3). Estimates for proportion of patients receiving goserelin in addition to ribociclib plus AI adjusted based on literature.	iDFS treatment mix of AI (as part of ribociclib plus AI) and the ET comparator based on those estimated by clinical experts for Population 4	[redacted]	[redacted]	989	0.391	0.398
		Proportion of patients receiving goserelin based on the NATALEE trial (ITT population; April 2024 data cut)	[redacted]	[redacted]	291	0.417	0.419
Treatment mix (DR health state)	45% of patients in the ribociclib plus AI arm of the model would receive retreatment with a CDK4/6 inhibitor in the ET-sensitive DR health state	90% of the ribociclib plus AI arms (and abemaciclib plus ET arm in Population 4) received CDK4/6 rechallenge as per ET arm (ET-sensitive DR health state)	[redacted]	[redacted]	5,838	0.321	0.366
		70% of the ribociclib plus AI arms (and abemaciclib plus ET arm in Population 4) received CDK4/6 rechallenge (ET-sensitive DR health state)	[redacted]	[redacted]	3,598	0.361	0.387
RDI	Same RDIs for AI (as part of ribociclib plus AI) and ET were assumed as per Population 1.	RDIs for all ETs (monotherapy and in combination with a CDK4/6 inhibitor),	[redacted]	[redacted]	566	0.411	0.415

Parameter	Base case	Scenario analysis	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
		goserelin and zoledronic acid, were assumed to be [redacted].					
Time on treatment extrapolation (AI [as part of ribociclib plus AI] and ET)	Weibull (R)	Loglogistic (R)	[redacted]	[redacted]	594	0.411	0.415
Maximum duration of treatment (AI/ET)	5 years	7 years	[redacted]	[redacted]	Dominant	0.465	0.454
		10 years	[redacted]	[redacted]	Dominant	0.532	0.500
Health state utility values	iDFS (on-treatment: 0.7620; off-treatment: 0.7367) and NMR (0.6818) health state utility values derived from EQ-5D data collected directly in NATALEE (ITT population)	iDFS and NMR health state utility values based on those used in TA810 (iDFS: 0.782; NMR: 0.760)	[redacted]	[redacted]	578	0.422	0.426
iDFS event distribution	Distribution of iDFS events for patients receiving ribociclib plus AI begins to linearly approach the distribution observed for ET patients, until the end of the treatment waning period	Distribution of iDFS events is assumed to remain constant over time	[redacted]	[redacted]	1,840	0.398	0.411

Abbreviations: AE: adverse event; AI: aromatase inhibitor; CDK4/6: cyclin dependent kinase 4/6; DR: distant recurrence; EQ-5D: EuroQoL-5dimensions; ET: endocrine therapy; HR: hazard ratio; iDFS: invasive disease-free survival; MAIC: matching-adjusted indirect comparison; NHB: net health benefit; NICE: National Institute for Health and Care Excellence; NMR: non-metastatic recurrence; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; R: restricted; RCS: restricted cubic spline; RDI: relative dose intensity; TA: technology appraisal; TTD: time-to-treatment discontinuation; U: unrestricted.

Population 4A (unweighted node-positive high-risk eligible for abemaciclib)

Probabilistic subgroup analysis results for the economic analysis of ribociclib plus AI vs ET and vs abemaciclib plus ET in Population 4A (unweighted node-positive high-risk eligible for abemaciclib) are presented in Table 28.

Table 28: Probabilistic subgroup analysis results: ribociclib plus AI vs ET and abemaciclib plus ET – Population 4A (unweighted node-positive high-risk eligible for abemaciclib)

	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	NHB £20,000 per QALY	NHB £30,000 per QALY
Ribociclib plus AI	[redacted]	15.01	[redacted]						
ET	[redacted]	14.32	[redacted]	[redacted]	-0.69	[redacted]	Dominated	0.75	0.68
Abemaciclib plus ET	[redacted]	14.99	[redacted]	[redacted]	-0.02	[redacted]	Dominated	2.15	1.44

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gained; NHB: net health benefit; QALYs: quality-adjusted life years.

A scatter plot showing the incremental costs and QALYs from the 1,000 iterations of the PSA for ribociclib plus AI vs ET in Population 4A (unweighted node-positive high-risk eligible for abemaciclib) is presented in Figure 21. A scatter plot showing the incremental costs and QALYs from the 1,000 iterations of the PSA for ribociclib plus AI vs abemaciclib plus ET in Population 4A (unweighted node-positive high-risk eligible for abemaciclib) is presented in Figure 22.

Figure 21: PSA scatter plot for ribociclib plus AI vs ET – Population 4A (unweighted node-positive high-risk eligible for abemaciclib)

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years; WTP: willingness to pay.

Figure 22: PSA scatter plot for ribociclib plus AI vs abemaciclib plus ET – Population 4A (unweighted node-positive high-risk eligible for abemaciclib)

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years; WTP: willingness to pay.

Scenario analysis

The results for all scenario analyses conducted in Population 4A (unweighted node-positive high-risk eligible for abemaciclib) vs ET and vs abemaciclib plus ET are presented in Table 29 and Table 30, respectively.

Table 29: Scenario analysis results vs ET – Population 4A (unweighted node-positive high-risk eligible for abemaciclib)

Parameter	Base case	Scenario analysis	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Base case			[redacted]	[redacted]	**Dominant**	**0.763**	**0.691**
iDFS extrapolation (ribociclib plus AI/ET)	Exponential	Gamma (U)	[redacted]	[redacted]	88,442*	1.983	1.129
		Gamma (R)	[redacted]	[redacted]	88,442*	1.983	1.129
Efficacy of tamoxifen vs AIs	HR: 1.10 (Liao *et al.* [2022])[21]	HR: 1.45 (Janni *et al.* [2023])[22]	[redacted]	[redacted]	Dominant	0.846	0.764
		HR: 1 (Assumption)	[redacted]	[redacted]	Dominant	0.740	0.670
Treatment waning	'Carryover benefit' of a constant treatment effect lasting up to 8 years, after which the treatment effect was modelled to wane, to the point at which the iDFS event rate was equal to general population mortality	Treatment effect assumed constant, and life-long, with no treatment waning	[redacted]	[redacted]	Dominant	0.923	0.819
		Treatment effect assumed constant up to 10 years	[redacted]	[redacted]	Dominant	0.791	0.714
		Treatment effect assumed constant up to 5 years	[redacted]	[redacted]	Dominant	0.712	0.646
		Treatment effect assumed constant up to 5 years, with treatment waning from Years 5–8 only	[redacted]	[redacted]	Dominant	0.344	0.324

Efficacy of post-progression therapies in DR health state	ET-resistant ML3 OS: Loglogistic (R)	ET-resistant ML3 OS: Weibull (R)	[redacted]	[redacted]	Dominant	0.652	0.640
	ET-resistant ML3 PFS: Lognormal (R)	ET-resistant ML3 PFS: Lognormal (U)	[redacted]	[redacted]	Dominant	0.753	0.683
	ET-resistant ML3 TTD: Gompertz (R)	ET-resistant ML3 TTD: RCS Weibull (R)	[redacted]	[redacted]	Dominant	0.696	0.646
	ET-sensitive ML2 OS: Log-logistic	ET-sensitive ML2 OS: Gamma	[redacted]	[redacted]	Dominant	0.813	0.731
	ET-sensitive ML2 PFS: Lognormal	ET-sensitive ML2 PFS: Exponential	[redacted]	[redacted]	Dominant	0.868	0.762
	ET-sensitive ML2 TTD: Exponential	ET-sensitive ML2 TTD: Weibull	[redacted]	[redacted]	Dominant	0.783	0.704
	Estimated HRs for PFS, OS and TTD in ET-sensitive DR health state for the given comparator vs ribociclib plus fulvestrant, based on published literature: For capecitabine: OS HR: 1.32; PFS HR: 1.64; TTD HR: as per PFS	PFS/OS/TTD HRs for capecitabine were assumed equivalent to letrozole/anastrozole	[redacted]	[redacted]	Dominant	0.784	0.681
Treatment mix of AI/ET (iDFS health state)	Aligned to clinical expert estimates for Population 4 from the September 2024 advisory board (see Appendix Q.3). The proportion of patients receiving goserelin in addition to abemaciclib plus ET in assumed to be equal to the proportion of patients receiving goserelin in addition to ribociclib plus AI.	iDFS treatment mix of AI (as part of ribociclib plus AI), ET (as part of abemaciclib plus ET) and the ET comparator based on those estimated by clinical experts for Population 1. Here, ET (as part of abemaciclib plus ET) was based on the treatment mix of AI as part of ribociclib plus AI) in Population 1	[redacted]	[redacted]	Dominant	0.787	0.711

		Proportion of patients receiving goserelin based on the NATALEE trial (ITT population; April 2024 data cut)	[redacted]	[redacted]	Dominant	0.761	0.689
Treatment mix (DR health state)	45% of patients in the ribociclib plus AI arm of the model would receive retreatment with a CDK4/6 inhibitor in the ET-sensitive DR health state	90% of the ribociclib plus AI arms (and abemaciclib plus ET arm in Population 4) received CDK4/6 rechallenge as per ET arm (ET-sensitive DR health state)	[redacted]	[redacted]	Dominant	0.662	0.635
		70% of the ribociclib plus AI arms (and abemaciclib plus ET arm in Population 4) received CDK4/6 rechallenge (ET-sensitive DR health state)	[redacted]	[redacted]	Dominant	0.707	0.659
RDI	RDI for abemaciclib calculated from RDI data for ribociclib (treatment pauses only) from the NATALEE trial (ITT population; April 2024 data cut). RDIs for ET (as part of abemaciclib plus ET) assumed to be 100%, based on what was assumed in TA810.[1] The RDIs for ribociclib plus AI and ET alone in assumed to be the same as Population 1.	RDIs for all ETs (monotherapy and in combination with a CDK4/6 inhibitor), goserelin and zoledronic acid, were assumed to be [redacted].	[redacted]	[redacted]	Dominant	0.764	0.691
		The RDI for abemaciclib assumed to equal the RDI for ribociclib, and the RDIs for ET (as part of abemaciclib plus ET) assumed to equal the RDIs for the relevant AIs in the ribociclib plus AI arm (with tamoxifen and zoledronic acid assumed to be [redacted]	[redacted]	[redacted]	Dominant	0.763	0.691

Time on treatment extrapolation (AI [as part of ribociclib plus AI], ET [as part of abemaciclib plus ET], and ET)	Lognormal (R)	RCS Lognormal (R)	[redacted]	[redacted]	Dominant	0.769	0.694
Time on treatment extrapolation for abemaciclib (as part of abemaciclib plus ET)	Based on KM derived from Rugo *et al.* (2022)[23]	Assumed equal to ribociclib TTD KM from NATALEE high-risk population up to 24 months	[redacted]	[redacted]	Dominant	0.763	0.691
Maximum duration of treatment (AI/ET)	5 years	7 years	[redacted]	[redacted]	Dominant	0.823	0.733
		10 years	[redacted]	[redacted]	Dominant	0.894	0.783
Health state utility values	iDFS (on-treatment: 0.7620; off-treatment: 0.7367) and NMR (0.6818) health state utility values derived from EQ-5D data collected directly in NATALEE (ITT population)	iDFS and NMR health state utility values based on those used in TA810 (iDFS: 0.782; NMR: 0.76)	[redacted]	[redacted]	Dominant	0.779	0.706
iDFS event distribution	Distribution of iDFS events for patients receiving ribociclib plus AI begins to linearly approach the distribution observed for ET patients, until the end of the treatment waning period	Distribution of iDFS events is assumed to remain constant over time	[redacted]	[redacted]	Dominant	0.752	0.688

Footnote: * This represents the ICER for abemaciclib plus ET vs ribociclib plus AI.
Abbreviations: AE: adverse event; AI: aromatase inhibitor; CDK4/6: cyclin dependent kinase 4/6; DR: distant recurrence; EQ-5D: EuroQoL-5dimensions; ET: endocrine therapy; HR: hazard ratio; iDFS: invasive disease-free survival; Incr: incremental; ITT: intention-to-treat; MAIC: matching-adjusted indirect comparison; NHB: net health benefit; NICE: National Institute for Health and Care Excellence; NMR: non-metastatic recurrence; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; (R): restricted; RCS: restricted cubic spline; RDI: relative dose intensity; TA: technology appraisal; TTD: time-to-treatment discontinuation; (U): unrestricted.

Table 30: Scenario analysis results vs abemaciclib plus ET – Population 4A (unweighted node-positive high-risk eligible for abemaciclib) –

Parameter	Base case	Scenario analysis	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Base case			[redacted]	[redacted]	**Dominant**	**2.190**	**1.462**
iDFS extrapolation (ribociclib plus AI/ET)	Exponential	Gamma (U)	[redacted]	[redacted]	Dominant	0.099	0.066
		Gamma (R)	[redacted]	[redacted]	Dominant	0.099	0.066
Efficacy of tamoxifen vs AIs	HR: 1.10 (Liao *et al.* [2022])[21]	HR: 1.45 (Janni *et al.* [2023])[22]	[redacted]	[redacted]	Dominant	2.190	1.462
		HR: 1 (Assumption)	[redacted]	[redacted]	Dominant	2.190	1.462
Treatment waning	'Carryover benefit' of a constant treatment effect lasting up to 8 years, after which the treatment effect was modelled to wane, to the point at which the iDFS event rate was equal to general population mortality	Treatment effect assumed constant, and life-long, with no treatment waning	[redacted]	[redacted]	Dominant	2.190	1.462
		Treatment effect assumed constant up to 10 years	[redacted]	[redacted]	Dominant	2.190	1.462
		Treatment effect assumed constant up to 5 years	[redacted]	[redacted]	Dominant	2.189	1.462
		Treatment effect assumed constant up to 5 years, with treatment waning from Years 5–8 only	[redacted]	[redacted]	Dominant	2.189	1.461
Efficacy of post-progression therapies in DR health state	ET-resistant ML3 OS: Loglogistic (R)	ET-resistant ML3 OS: Weibull (R)	[redacted]	[redacted]	Dominant	2.190	1.461
	ET-resistant ML3 PFS: Lognormal (R)	ET-resistant ML3 PFS: Lognormal (U)	[redacted]	[redacted]	Dominant	2.189	1.462
	ET-resistant ML3 TTD: Gompertz (R)	ET-resistant ML3 TTD: RCS Weibull (R)	[redacted]	[redacted]	Dominant	2.193	1.464

	ET-sensitive ML2 OS: Log-logistic	ET-sensitive ML2 OS: Gamma	[redacted]	[redacted]	Dominant	2.190	1.462
	ET-sensitive ML2 PFS: Lognormal	ET-sensitive ML2 PFS: Exponential	[redacted]	[redacted]	Dominant	2.190	1.462
	ET-sensitive ML2 TTD: Exponential	ET-sensitive ML2 TTD: Weibull	[redacted]	[redacted]	Dominant	2.190	1.462
	Estimated HRs for PFS, OS and TTD in ET-sensitive DR health state for the given comparator vs ribociclib plus fulvestrant, based on published literature: For capecitabine: OS HR: 1.32; PFS HR: 1.64; TTD HR: as per PFS	PFS/OS/TTD HRs for capecitabine were assumed equivalent to letrozole/anastrozole	[redacted]	[redacted]	Dominant	2.190	1.462
Treatment mix of AI/ET (iDFS health state)	Aligned to clinical expert estimates for Population 4 from the September 2024 advisory board (see Appendix Q.3). The proportion of patients receiving goserelin in addition to abemaciclib plus ET in assumed to be equal to the proportion of patients receiving goserelin in addition to ribociclib plus AI.	iDFS treatment mix of AI (as part of ribociclib plus AI), ET (as part of abemaciclib plus ET) and the ET comparator based on those estimated by clinical experts for Population 1. Here, ET (as part of abemaciclib plus ET) was based on the treatment mix of AI as part of ribociclib plus AI) in Population 1	[redacted]	[redacted]	Dominant	2.189	1.462
		Proportion of patients receiving goserelin based on the NATALEE trial (ITT population; April 2024 data cut)	[redacted]	[redacted]	Dominant	2.151	1.436
	45% of patients in the ribociclib plus AI arm of	90% of the ribociclib plus AI arms (and abemaciclib	[redacted]	[redacted]	Dominant	2.190	1.462

Treatment mix (DR health state)	the model would receive retreatment with a CDK4/6 inhibitor in the ET-sensitive DR health state	plus ET arm in Population 4) received CDK4/6 rechallenge as per ET arm (ET-sensitive DR health state)					
		70% of the ribociclib plus AI arms (and abemaciclib plus ET arm in Population 4) received CDK4/6 rechallenge (ET-sensitive DR health state)	[redacted]	[redacted]	Dominant	2.190	1.462
RDI	RDI for abemaciclib calculated from RDI data for ribociclib (treatment pauses only) from the NATALEE trial (ITT population; April 2024 data cut). RDIs for ET (as part of abemaciclib plus ET) assumed to be 100%, based on what was assumed in TA810.[1] The RDIs for ribociclib plus AI and ET alone in assumed to be the same as Population 1.	RDIs for all ETs (monotherapy and in combination with a CDK4/6 inhibitor), goserelin and zoledronic acid, were assumed to be [redacted].	[redacted]	[redacted]	Dominant	2.190	1.462
		The RDI for abemaciclib assumed to equal the RDI for ribociclib, and the RDIs for ET (as part of abemaciclib plus ET) assumed to equal the RDIs for the relevant AIs in the ribociclib plus AI arm (with tamoxifen and zoledronic acid assumed to be [redacted]	[redacted]	[redacted]	Dominant	1.743	1.165
Time on treatment extrapolation (AI [as part of ribociclib plus AI], ET [as part of abemaciclib	Lognormal (R)	RCS Lognormal (R)	[redacted]	[redacted]	Dominant	2.191	1.463

plus ET], and ET)							
Time on treatment extrapolation for abemaciclib (as part of abemaciclib plus ET)	Based on KM derived from Rugo *et al.* (2022)[23]	Assumed equal to ribociclib TTD KM from NATALEE high-risk population up to 24 months	[redacted]	[redacted]	Dominant	2.143	1.431
Maximum duration of treatment (AI/ET)	5 years	7 years	[redacted]	[redacted]	Dominant	2.171	1.451
		10 years	[redacted]	[redacted]	Dominant	2.148	1.438
Health state utility values	iDFS (on-treatment: 0.7620; off-treatment: 0.7367) and NMR (0.6818) health state utility values derived from EQ-5D data collected directly in NATALEE (ITT population)	iDFS and NMR health state utility values based on those used in TA810 (iDFS: 0.782; NMR: 0.76)	[redacted]	[redacted]	Dominant	2.190	1.462
iDFS event distribution	Distribution of iDFS events for patients receiving ribociclib plus AI begins to linearly approach the distribution observed for ET patients, until the end of the treatment waning period	Distribution of iDFS events is assumed to remain constant over time	[redacted]	[redacted]	Dominant	2.190	1.462

Abbreviations: AE: adverse event; AI: aromatase inhibitor; CDK4/6: cyclin dependent kinase 4/6; DR: distant recurrence; EQ-5D: EuroQoL-5dimensions; ET: endocrine therapy; HR: hazard ratio; iDFS: invasive disease-free survival; Incr: incremental; ITT: intention-to-treat; MAIC: matching-adjusted indirect comparison; NHB: net health benefit; NICE: National Institute for Health and Care Excellence; NMR: non-metastatic recurrence; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; (R): restricted; RCS: restricted cubic spline; RDI: relative dose intensity; TA: technology appraisal; TTD: time-to-treatment discontinuation; (U): unrestricted **Abbreviations:** AE: adverse event; AI: aromatase inhibitor; CDK4/6: cyclin dependent kinase 4/6; DR: distant recurrence; EQ-5D: EuroQoL-5dimensions; ET: endocrine therapy; HR: hazard ratio; iDFS: invasive disease-free survival; MAIC: matching-adjusted indirect comparison; NICE: National Institute for Health and Care Excellence; NMR: non-metastatic recurrence; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; R: restricted; RCS: restricted cubic spline; RDI: relative dose intensity; TA: technology appraisal; TTD: time-to-treatment discontinuation; U: unrestricted..

Population 4B (weighted node-positive high-risk eligible for abemaciclib)

Probabilistic subgroup analysis results for the economic analysis of ribociclib plus AI vs ET and vs abemaciclib plus ET in Population 4B (weighted node-positive high-risk eligible for abemaciclib) are presented in Table 31.

Table 31: Probabilistic subgroup analysis results: ribociclib plus AI vs ET and abemaciclib plus ET – Population 4B (weighted node-positive high-risk eligible for abemaciclib)

	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	NHB £20,000 per QALY	NHB £30,000 per QALY
Ribociclib plus AI	[redacted]	15.46	[redacted]						
ET	[redacted]	14.67	[redacted]	[redacted]	-0.80	[redacted]	Dominated	0.81	0.74
Abemaciclib plus ET	[redacted]	15.45	[redacted]	[redacted]	-0.02	[redacted]	Dominated	2.16	1.44

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gained; NHB: net health benefit; QALYs: quality-adjusted life years.

A scatter plot showing the incremental costs and QALYs from the 1,000 iterations of the PSA for ribociclib plus AI vs ET in Population 4B (weighted node-positive high-risk eligible for abemaciclib) is presented in Figure 23. A scatter plot showing the incremental costs and QALYs from the 1,000 iterations of the PSA for ribociclib plus AI vs abemaciclib plus ET in Population 4B (weighted node-positive high-risk eligible for abemaciclib) is presented in Figure 24.

Figure 23: PSA scatter plot for ribociclib plus AI vs ET – Population 4B (weighted node-positive high-risk eligible for abemaciclib)

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years; WTP: willingness to pay.

Figure 24: PSA scatter plot for ribociclib plus AI vs abemaciclib plus ET – Population 4B (weighted node-positive high-risk eligible for abemaciclib)

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years; WTP: willingness to pay.

Scenario analysis

The results for all scenario analyses conducted in Population 4B (weighted node-positive high-risk eligible for abemaciclib) vs ET and vs abemaciclib plus ET are presented in Table 32 and Table 33, respectively.

Table 32: Scenario analysis results vs ET – Population 4B (weighted node-positive high-risk eligible for abemaciclib)

Parameter	Base case	Scenario analysis	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Base case			[redacted]	[redacted]	**Dominant**	**0.830**	**0.763**
iDFS extrapolation (ribociclib plus AI/ET)	Exponential (MAIC)	Gamma (U) (MAIC)	[redacted]	[redacted]	Dominant	0.988	0.903
		Gamma (R) (MAIC)	[redacted]	[redacted]	Dominant	0.825	0.759
Efficacy of tamoxifen vs AIs	HR: 1.10 (Liao *et al.* [2022])[21]	HR: 1.45 (Janni *et al.* [2023])[22]	[redacted]	[redacted]	Dominant	0.909	0.833
		HR: 1 (Assumption)	[redacted]	[redacted]	Dominant	0.807	0.742
Treatment waning	'Carryover benefit' of a constant treatment effect lasting up to 8 years, after which the treatment effect was modelled to wane, to the point at which the iDFS event rate was equal to general population mortality	Treatment effect assumed constant, and life-long, with no treatment waning	[redacted]	[redacted]	Dominant	1.038	0.929
		Treatment effect assumed constant up to 10 years	[redacted]	[redacted]	Dominant	0.863	0.792
		Treatment effect assumed constant up to 5 years	[redacted]	[redacted]	Dominant	0.768	0.709
		Treatment effect assumed constant up to 5 years, with treatment waning from Years 5–8 only	[redacted]	[redacted]	Dominant	0.363	0.354
Efficacy of post-	ET-resistant ML3 OS: Loglogistic (R)	ET-resistant ML3 OS: Weibull (R)	[redacted]	[redacted]	Dominant	0.727	0.718

progression therapies in DR health state	ET-resistant ML3 PFS: Lognormal (R)	ET-resistant ML3 PFS: Lognormal (U)	[redacted]	[redacted]	Dominant	0.820	0.756
	ET-resistant ML3 TTD: Gompertz (R)	ET-resistant ML3 TTD: RCS Weibull (R)	[redacted]	[redacted]	Dominant	0.767	0.721
	ET-sensitive ML2 OS: Log-logistic	ET-sensitive ML2 OS: Gamma	[redacted]	[redacted]	Dominant	0.878	0.803
	ET-sensitive ML2 PFS: Lognormal	ET-sensitive ML2 PFS: Exponential	[redacted]	[redacted]	Dominant	0.934	0.834
	ET-sensitive ML2 TTD: Exponential	ET-sensitive ML2 TTD: Weibull	[redacted]	[redacted]	Dominant	0.850	0.776
	Estimated HRs for PFS, OS and TTD in ET-sensitive DR health state for the given comparator vs ribociclib plus fulvestrant, based on published literature: For capecitabine: OS HR: 1.32; PFS HR: 1.64; TTD HR: as per PFS	PFS/OS/TTD HRs for capecitabine were assumed equivalent to letrozole/anastrozole	[redacted]	[redacted]	Dominant	0.850	0.753
Treatment mix of AI/ET (iDFS health state)	Aligned to clinical expert estimates for Population 4 from the September 2024 advisory board (see Appendix Q.3). The proportion of patients receiving goserelin in addition to abemaciclib plus ET in assumed to be equal to the proportion of patients receiving goserelin in addition to ribociclib plus AI.	iDFS treatment mix of AI (as part of ribociclib plus AI), ET (as part of abemaciclib plus ET) and the ET comparator based on those estimated by clinical experts for Population 1. Here, ET (as part of abemaciclib plus ET) was based on the treatment mix of AI as part of ribociclib plus AI) in Population 1	[redacted]	[redacted]	Dominant	0.852	0.783
		Proportion of patients receiving goserelin based on the NATALEE trial	[redacted]	[redacted]	Dominant	0.826	0.760

		(ITT population; April 2024 data cut)					
Treatment mix (DR health state)	45% of patients in the ribociclib plus AI arm of the model would receive retreatment with a CDK4/6 inhibitor in the ET-sensitive DR health state	90% of the ribociclib plus AI arms (and abemaciclib plus ET arm in Population 4) received CDK4/6 rechallenge as per ET arm (ET-sensitive DR health state)	[redacted]	[redacted]	Dominant	0.732	0.709
		70% of the ribociclib plus AI arms (and abemaciclib plus ET arm in Population 4) received CDK4/6 rechallenge (ET-sensitive DR health state)	[redacted]	[redacted]	Dominant	0.775	0.733
RDI	RDI for abemaciclib calculated from RDI data for ribociclib (treatment pauses only) from the NATALEE trial (ITT population; April 2024 data cut). RDIs for ET (as part of abemaciclib plus ET) assumed to be 100%, based on what was assumed in TA810.[1] The RDIs for ribociclib plus AI and ET alone in assumed to be the same as Population 1.	RDIs for all ETs (monotherapy and in combination with a CDK4/6 inhibitor), goserelin and zoledronic acid, were assumed to be [redacted].	[redacted]	[redacted]	Dominant	0.830	0.763
		The RDI for abemaciclib assumed to equal the RDI for ribociclib, and the RDIs for ET (as part of abemaciclib plus ET) assumed to equal the RDIs for the relevant AIs in the ribociclib plus AI arm (with tamoxifen and zoledronic acid assumed to be [redacted]	[redacted]	[redacted]	Dominant	0.830	0.763
Time on treatment extrapolation (AI [as part of	Lognormal (R)	RCS Lognormal (R)	[redacted]	[redacted]	Dominant	0.830	0.763

ribociclib plus AI], ET [as part of abemaciclib plus ET], and ET)							
Time on treatment extrapolation for abemaciclib (as part of abemaciclib plus ET)	Based on KM derived from Rugo *et al.* (2022)[23]	Assumed equal to ribociclib TTD KM from NATALEE high-risk population up to 24 months	[redacted]	[redacted]	Dominant	0.830	0.763
Maximum duration of treatment (AI/ET)	5 years	7 years	[redacted]	[redacted]	Dominant	0.885	0.803
		10 years	[redacted]	[redacted]	Dominant	0.953	0.851
Health state utility values	iDFS (on-treatment: 0.7620; off-treatment: 0.7367) and NMR (0.6818) health state utility values derived from EQ-5D data collected directly in NATALEE (ITT population)	iDFS and NMR health state utility values based on those used in TA810 (iDFS: 0.782; NMR: 0.76)	[redacted]	[redacted]	Dominant	0.847	0.780
iDFS event distribution	Distribution of iDFS events for patients receiving ribociclib plus AI begins to linearly approach the distribution observed for ET patients, until the end of the treatment waning period	Distribution of iDFS events is assumed to remain constant over time	[redacted]	[redacted]	Dominant	0.817	0.759

Abbreviations: AE: adverse event; AI: aromatase inhibitor; CDK4/6: cyclin dependent kinase 4/6; DR: distant recurrence; EQ-5D: EuroQoL-5dimensions; ET: endocrine therapy; HR: hazard ratio; iDFS: invasive disease-free survival; Incr: incremental; ITT: intention-to-treat; MAIC: matching-adjusted indirect comparison; NHB: net health benefit; NICE: National Institute for Health and Care Excellence; NHB: net health benefit; NMR: non-metastatic recurrence; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; (R): restricted; RCS: restricted cubic spline; RDI: relative dose intensity; TA: technology appraisal; TTD: time-to-treatment discontinuation; (U): unrestricted.

Table 33: Scenario analysis results vs abemaciclib plus ET – Population 4B (weighted node-positive high-risk eligible for abemaciclib) –

Parameter	Base case	Scenario analysis	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Base case			[redacted]	[redacted]	**Dominant**	**2.203**	**1.471**
iDFS extrapolation (ribociclib plus AI/ET)	Exponential (MAIC)	Gamma (U) (MAIC)	[redacted]	[redacted]	Dominant	2.204	1.471
		Gamma (R) (MAIC)	[redacted]	[redacted]	Dominant	2.203	1.471
Efficacy of tamoxifen vs AIs	HR: 1.10 (Liao *et al.* [2022])[21]	HR: 1.45 (Janni *et al.* [2023])[22]	[redacted]	[redacted]	Dominant	2.203	1.471
		HR: 1 (Assumption)	[redacted]	[redacted]	Dominant	2.203	1.471
Treatment waning	'Carryover benefit' of a constant treatment effect lasting up to 8 years, after which the treatment effect was modelled to wane, to the point at which the iDFS event rate was equal to general population mortality	Treatment effect assumed constant, and life-long, with no treatment waning	[redacted]	[redacted]	Dominant	2.203	1.471
		Treatment effect assumed constant up to 10 years	[redacted]	[redacted]	Dominant	2.203	1.471
		Treatment effect assumed constant up to 5 years	[redacted]	[redacted]	Dominant	2.203	1.471
		Treatment effect assumed constant up to 5 years, with treatment waning from Years 5–8 only	[redacted]	[redacted]	Dominant	2.202	1.470
Efficacy of post-progression therapies in DR health state	ET-resistant ML3 OS: Loglogistic (R)	ET-resistant ML3 OS: Weibull (R)	[redacted]	[redacted]	Dominant	2.203	1.470
	ET-resistant ML3 PFS: Lognormal (R)	ET-resistant ML3 PFS: Lognormal (U)	[redacted]	[redacted]	Dominant	2.203	1.471
	ET-resistant ML3 TTD: Gompertz (R)	ET-resistant ML3 TTD: RCS Weibull (R)	[redacted]	[redacted]	Dominant	2.207	1.473

	ET-sensitive ML2 OS: Log-logistic	ET-sensitive ML2 OS: Gamma	[redacted]	[redacted]	Dominant	2.203	1.471
	ET-sensitive ML2 PFS: Lognormal	ET-sensitive ML2 PFS: Exponential	[redacted]	[redacted]	Dominant	2.203	1.471
	ET-sensitive ML2 TTD: Exponential	ET-sensitive ML2 TTD: Weibull	[redacted]	[redacted]	Dominant	2.203	1.471
	Estimated HRs for PFS, OS and TTD in ET-sensitive DR health state for the given comparator vs ribociclib plus fulvestrant, based on published literature: For capecitabine: OS HR: 1.32; PFS HR: 1.64; TTD HR: as per PFS	PFS/OS/TTD HRs for capecitabine were assumed equivalent to letrozole/anastrozole	[redacted]	[redacted]	Dominant	2.203	1.471
Treatment mix of AI/ET (iDFS health state)	Aligned to clinical expert estimates for Population 4 from the September 2024 advisory board (see Appendix Q.3). The proportion of patients receiving goserelin in addition to abemaciclib plus ET in assumed to be equal to the proportion of patients receiving goserelin in addition to ribociclib plus AI.	iDFS treatment mix of AI (as part of ribociclib plus AI), ET (as part of abemaciclib plus ET) and the ET comparator based on those estimated by clinical experts for Population 1. Here, ET (as part of abemaciclib plus ET) was based on the treatment mix of AI as part of ribociclib plus AI) in Population 1	[redacted]	[redacted]	Dominant	2.203	1.471
		Proportion of patients receiving goserelin based on the NATALEE trial (ITT population; April 2024 data cut)	[redacted]	[redacted]	Dominant	2.164	1.445
	45% of patients in the ribociclib plus AI arm of	90% of the ribociclib plus AI arms (and abemaciclib	[redacted]	[redacted]	Dominant	2.203	1.471

Treatment mix (DR health state)	the model would receive retreatment with a CDK4/6 inhibitor in the ET-sensitive DR health state	plus ET arm in Population 4) received CDK4/6 rechallenge as per ET arm (ET-sensitive DR health state)					
		70% of the ribociclib plus AI arms (and abemaciclib plus ET arm in Population 4) received CDK4/6 rechallenge (ET-sensitive DR health state)	[redacted]	[redacted]	Dominant	2.203	1.471
RDI	RDI for abemaciclib calculated from RDI data for ribociclib (treatment pauses only) from the NATALEE trial (ITT population; April 2024 data cut). RDIs for ET (as part of abemaciclib plus ET) assumed to be 100%, based on what was assumed in TA810.[1] The RDIs for ribociclib plus AI and ET alone in assumed to be the same as Population 1.	RDIs for all ETs (monotherapy and in combination with a CDK4/6 inhibitor), goserelin and zoledronic acid, were assumed to be [redacted].	[redacted]	[redacted]	Dominant	2.204	1.471
		The RDI for abemaciclib assumed to equal the RDI for ribociclib, and the RDIs for ET (as part of abemaciclib plus ET) assumed to equal the RDIs for the relevant AIs in the ribociclib plus AI arm (with tamoxifen and zoledronic acid assumed to be [redacted]	[redacted]	[redacted]	Dominant	1.757	1.174
Time on treatment extrapolation (AI [as part of ribociclib plus AI], ET [as part of abemaciclib	Lognormal (R)	RCS Lognormal (R)	[redacted]	[redacted]	Dominant	2.203	1.471

plus ET], and ET)							
Time on treatment extrapolation for abemaciclib (as part of abemaciclib plus ET)	Based on KM derived from Rugo *et al.* (2022)[23]	Assumed equal to ribociclib TTD KM from NATALEE high-risk population up to 24 months	[redacted]	[redacted]	Dominant	2.107	1.407
Maximum duration of treatment (AI/ET)	5 years	7 years	[redacted]	[redacted]	Dominant	2.187	1.461
		10 years	[redacted]	[redacted]	Dominant	2.166	1.449
Health state utility values	iDFS (on-treatment: 0.7620; off-treatment: 0.7367) and NMR (0.6818) health state utility values derived from EQ-5D data collected directly in NATALEE (ITT population)	iDFS and NMR health state utility values based on those used in TA810 (iDFS: 0.782; NMR: 0.76)	[redacted]	[redacted]	Dominant	2.203	1.471
iDFS event distribution	Distribution of iDFS events for patients receiving ribociclib plus AI begins to linearly approach the distribution observed for ET patients, until the end of the treatment waning period	Distribution of iDFS events is assumed to remain constant over time	[redacted]	[redacted]	Dominant	2.203	1.471

Footnote: [a] This represents the ICER for abemaciclib plus ET vs ribociclib plus AI.
Abbreviations: AE: adverse event; AI: aromatase inhibitor; CDK4/6: cyclin dependent kinase 4/6; DR: distant recurrence; EQ-5D: EuroQoL-5dimensions; ET: endocrine therapy; HR: hazard ratio; iDFS: invasive disease-free survival; Incr: incremental; ITT: intention-to-treat; MAIC: matching-adjusted indirect comparison; NHB: net health benefit; NICE: National Institute for Health and Care Excellence; NMR: non-metastatic recurrence; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; (R): restricted; RCS: restricted cubic spline; RDI: relative dose intensity; TA: technology appraisal; TTD: time-to-treatment discontinuation; (U): unrestricted.

References

1. NICE. Abemaciclib with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence [TA810]. 2022. Available from: https://www.nice.org.uk/guidance/ta810. Accessed: 11 October 2024.
2. Novartis. Data on file: Additional resources for Clarification questions. 2024.
3. Rohatgi A. WebPlotDigitizer v4.8. 2023. Available at: https://apps.automeris.io/wpd4/. Accessed: 03 October 2023.
4. Guyot P, Ades AE, Ouwens MJNM, et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Medical Research Methodology 2012;12:9.
5. Phillippo DM, Ades AE, Dias S, et al. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submission to NICE. 2016. Available from: http://www.nicedsu.org.uk. Accessed: 23 October 2023.
6. Johnston SRD, Harbeck N, Hegg R, et al. Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE). J Clin Oncol 2020;38:3987-3998.
7. Hudis CA, Barlow WE, Costantino JP, et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. J Clin Oncol 2007;25:2127-32.
8. Rastogi P, O'Shaughnessy J, Martin M, et al. Adjuvant Abemaciclib Plus Endocrine Therapy for Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative, High-Risk Early Breast Cancer: Results From a Preplanned monarchE Overall Survival Interim Analysis, Including 5-Year Efficacy Outcomes. Journal of Clinical Oncology 2024;42:987-993.
9. Novartis. Data on File. Programming code for A9 (STC for iDFS). 2024.
10. Novartis. Data on File. Programming code for A10 (Time varying HR). 2024.
11. NICE. NG101. Early and locally advanced breast cancer: diagnosis and management. 2018. Available from: https://www.nice.org.uk/guidance/ng101/resources/early-and-locally-advanced-breast-cancer-diagnosis-and-management-pdf-66141532913605. Accessed: April 2023.
12. Novartis. Data on File: Draft Ribociclib SmPc. 2024.
13. Novartis. Data on File: NATALEE Protocol. 2020.
14. Novartis. Data on File: NATALEE Clinical Study Report April 2024 Data Cut. 2024.
15. Novartis. Data on File. MONALEESA-3 trial statistical analysis report.
16. Novartis. Data on File. MONALEESA-2 trial statistical analysis report.
17. Novartis. Data on File. MONALEESA-2 trial CSR.
18. Novartis. Data on File. MONALEESA-3 trial CSR.
19. Neven P, Fasching PA, Chia S, et al. Updated overall survival from the MONALEESA-3 trial in postmenopausal women with HR+/HER2− advanced breast cancer receiving first-line ribociclib plus fulvestrant. Breast Cancer Research 2023;25:103.
20. Centre for Reviews and Dissemination University of York. Systematic reviews: CRD's guidance for undertaking reviews in health care. 2009. Available from: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf. Accessed: 29 August 2023.
21. Liao H, Pei W, Zhong J, et al. Efficacy and Safety of Initial 5 Years of Adjuvant Endocrine Therapy in Postmenopausal Hormone Receptor-Positive Breast Cancer: A Systematic Review and Network Meta-Analysis. Front Pharmacol 2022;13:886954.
22. Janni W, Untch M, Harbeck N, et al. P1 02 01: Comparing the efficacy of aromatase inhibitors vs tamoxifen in hormone receptor positive, human epidermal growth factor receptor 2 negative early breast cancer: a systematic review and trial level meta analysis. San Antonio Breast Cancer Symposium December 6 10, 2022.
23. Rugo HS, O'Shaughnessy J, Boyle F, et al. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: safety and patient-reported outcomes from the monarchE study. Ann Oncol 2022;33:616-627.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ribociclib with an aromatase inhibitor for adjuvant treatment of hormone receptor-positive, HER2-negative early breast cancer [ID6153]

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	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.**	In the last 12 months (from October 2023), Breast Cancer Now has received the following funding from manufacturers listed in the appraisal matrix. Please note, Breast Cancer Now does not receive any pharmaceutical funding for our Policy, Evidence and Influencing work. • In May 2024, £15,000 from Eli Lilly towards our nursing conference • In April 2024, £15,000 from Novartis towards our nursing conference • In March 2024, £50,000 from Novartis to support a research project 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 October 2023), this has included the following listed on this appraisal matrix: - £3,000 from AstraZeneca towards the UKIBCS 2024 - £50,000 from Novartis towards to UKIBCS 2024
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 utilise our various networks of people affected by breast cancer to gather information about patient experience, including our online Breast Cancer Now Forum, as well as our online and face to face services.

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?	A diagnosis of breast cancer can cause considerable anxiety to the patient as well as their family and friends. The initial diagnosis can be extremely shocking and have a major impact on the person's emotional wellbeing. In the longer-term, the fear of breast cancer returning or spreading to other parts of the body (such as the bone, liver, lung and brain), which is known as secondary breast cancer and is incurable, can be extremely frightening for patients and their loved ones. One patient we spoke to for this appraisal described herself as feeling like a 'sitting duck' following her treatment for primary breast cancer. She said that the fear of recurrence had left her in 'a very bad headspace'. Breast cancer patients also tell us about the impact of the disease on their day to day lives, for example the side effects of treatment and visits to hospital taking a toll on their general wellbeing. These impacts may be both physical and psychological and may last for many years beyond the completion of treatment. Treatment for breast cancer can have a number of side effects which can have a significant impact on everyday activities, ability to work and relationships. Hormone-receptor positive breast cancer is the most common type of breast cancer, and up to four in five or 80% of breast cancers are oestrogen receptor positive (ER+). This accounts for around 44,000 cases in the UK each year. A new adjuvant treatment would provide a further treatment option for women with hormone receptor positive, HER2-negative primary breast cancer. It is estimated that 15-20% of patients with hormone receptor positive cancer may experience a recurrence. The risk of recurrence is higher in those with node-positive, high risk primary breast cancer. Those with node negative primary breast cancer have a lower risk of recurrence, but account for a larger population of patients. New treatments which help to reduce the chances of breast cancer returning are crucial for both these groups. Breast cancer recurrence can occur many years after treatment. Living with this uncertainty can impact a patient's psychological wellbeing significantly for many years.

Current treatment of the condition in the NHS

1.

7. What do patients or carers think of current treatments and care available on the NHS?	For many years chemotherapy, followed by hormone treatment was the mainstay of drug treatment for this group of patients to help reduce the risk of the breast cancer returning. In line with the NICE early and locally advanced guidelines, men and premenopausal women will be offered tamoxifen as an adjuvant (following surgery) endocrine therapy. Premenopausal women could also be offered an aromatase inhibitor with ovarian suppression. An aromatase inhibitor (letrozole, anastrozole or exemestane) will be offered as the initial adjuvant endocrine therapy for postmenopausal women with ER positive breast cancer. Current guidelines recommend that extended hormone therapy might be considered for pre-menopausal and post-menopausal women with ER positive breast cancer depending on their risk of recurrence. Some people will be given tamoxifen, aromatase inhibitors, or a combination of these for up to 10 years. A patient we spoke to as part of this appraisal described feeling that “the treatments haven’t moved on for many years…the same drugs they were using 30 years ago. Things are a bit stagnant.” All treatments have side effects. Everyone reacts differently to drugs and some people have more side effects than others. Hormone therapy can have several side effects. These can include menopausal symptoms, joint/muscle pain and fatigue, that can make it difficult for women to complete the recommended course of therapy. Additionally, side effects such as vaginal dryness and loss of libido can be very distressing and may be difficult for the patient to talk about so will often go untreated. Research has shown that compliance with hormone therapy can be low due to several factors, including those mentioned above. Since June 2022, adjuvant abemaciclib has been available on the NHS in England for certain women with hormone receptor positive, HER2 negative primary breast cancer. It is taken for two years alongside hormone therapy and people will then continue having hormone therapy for up to a total of ten years. For patients this was an important step-change in the drug options available for this group of patients - offering another option to further reduce the risk of the disease returning. At the time of its approval it was estimated that it would benefit around 4,000 people. Abemaciclib is also associated with side-effects, including diarrhoea. Some people will be eligible for adjuvant olaparib, a PARP inhibitor, which has been approved for treating women with BRCA positive, HER2-negative primary breast cancer since April 2023. This includes women with hormone receptor positive breast cancer. The approval of olaparib has been hugely welcomed, as it's a potentially life-saving treatment. Crucially, olaparib can reduce the risk of people's cancer returning or

	progressing to incurable secondary breast cancer and stop people dying from breast cancer. At the time of its approval it was estimated that around 300 people per year would benefit from this treatment. Olaparib is also associated with side-effects, including nausea, fatigue and diarrhoea. Our helpline received many calls when both abemaciclib and olaparib were approved, from people wanting to know if they would be eligible for or benefit from these treatments- showing that patients are keen to access new therapies that may reduce the risk of their breast cancer returning.
8. Is there an unmet need for patients with this condition?	The introduction of adjuvant ribociclib could potentially enable a wider group of patients with early breast cancer to access a CDK4/6 inhibitor than are currently eligible for adjuvant abemaciclib. The NATALEE trial for ribociclib includes patients who are both lymph node positive and people who are lymph node negative. The approval of ribociclib could allow more people access to a CKD4/6 inhibitor for primary hormone receptor positive, HER2-negative breast cancer. Ribociclib and abemaciclib have different side effect profiles, meaning if ribociclib was approved patients and clinicians would have more treatment options available.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	In general, more adjuvant treatment options that help to reduce the risk of breast cancer recurrence would be very much welcomed by patients. They could help prevent patients' needing further treatment if their cancer were to return or spread, and the associated physical and psychological impacts on their quality of life, as well as helping to reduce patients', and their families' anxiety about their cancer returning, by providing the most effective treatment options for their cancer diagnosis. This can help to reduce anxiety and improve patients' physical and psychological quality of life. The addition of a different CDK 4/6 inhibitor as an option for patients at this point in the pathway may be of benefit to those experiencing side-effects from abemaciclib. Data from the NATALEE clinical trial published in September 2024 showed that ribociclib in combination with endocrine therapy reduced the risk of recurrence by 28.5% compared to endocrine therapy alone. The 4 year invasive disease free survival rate in the intention to treat population was 88.5% for ribocliclib and endocrine therapy, compared to 83.6 for endocrine therapy alone. For node-negative patients, who do not currently have access to a CDK4/6 inhibitor through the NHS, ribociclib and endocrine therapy was associated with 4yr invasive disease free survival rate of 92.1%, compared to 87% for endocrine therapy alone. Ribociclib is taken as a tablet, meaning it can be taken at home and does not require patients to spend more time in hospital. A patient we spoke to for this appraisal who is accessing adjuvant ribociclib on private medical insurance described it as "a safety blanket to catch anything… I feel lucky to be able to access it." She also said that the treatment "is quite a low burden... I don't have to go into hospital, to go for an infusion or anything like that".

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	As with all breast cancer treatments, patients can experience side effects. Everyone reacts differently to drugs and some people have more side effects than others. The most common adverse effects experienced by patients on ribociclib were neutropenia and joint pain. Rates of gastrointestinal adverse effects and fatigue were low. In the trial adverse events reported included neutropenia, liver related issues and QT interval prolongation. Adverse events were common in trial participants - at least one adverse event occurred in 98% of people in the ribociclib and AI group and 87% in the AI only group. However only 18% of patients had to stop treatment. A patient we spoke to who is accessing adjuvant ribociclib through private medical insurance said that she had experienced some fatigue while on the drug, but "I've been able to tolerate the drug well, I can work full time, I can contribute to society and do a lot." Most patients understand that all treatments may have some side effects. Whilst it is important patients are properly informed of any adverse effects, most patients find the benefits of a new treatment outweigh the risk of adverse effects.

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.	When used to treat secondary breast cancer, ribociclib is unsuitable for some patients with heart conditions due to QT prolongation, and as a secondary drug it required monitoring via an ECG for some patients. Some people who are not eligible for other options, such as abemaciclib, will be able to have ribociclib.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Not that we are aware of

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• A diagnosis of breast cancer can have a major impact on patients' day-to-day lives. The physical and psychological impacts of breast cancer may last for many years beyond initial treatment - fear of recurrence in particular can significantly impact patients' psychological wellbeing for many years to come. It is estimated that 15-20% of people with HR-positive primary breast cancer will experience a recurrence. • This group of patients has for many years been treated with chemotherapy and hormone therapy (either tamoxifen or an aromatase inhibitor). In recent years more treatments have been made available at this stage in the pathway, including adjuvant abemaciclib and adjuvant olaparib, but not all patients will be eligible to receive these treatments. • Patients would welcome the introduction of more adjuvant treatment options that help to reduce the risk of recurrence. Access to a different CDK 4/6 inhibitor would be especially welcomed by those who cannot currently access adjuvant abemaciclib, potentially because they are node negative, as well as those experiencing side-effects from abemaciclib. • Data from the NATALEE clinical trial published in September 2024 showed that ribociclib in combination with endocrine therapy reduced the risk of recurrence by 28.5% compared to endocrine therapy alone. The 4 year invasive disease free survival rate in the intention to treat population was 88.5% for ribocliclib and endocrine therapy, compared to 83.6 for endocrine therapy alone. • All breast cancer treatments have side-effects - the most common adverse effects experienced by patients on ribociclib were neutropenia and joint pain. Whilst it is important patients are properly informed of any adverse effects, most patients find the benefits of a new treatment outweigh the risk of adverse effects.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ribociclib with an aromatase inhibitor for adjuvant treatment of hormone receptor-positive, HER2-negative early breast cancer [ID6153]

Professional 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 the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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 13 pages.

NICE National Institute for Health and Care Excellence

About you

NICE National Institute for Health and Care Excellence

1. Your name	[redacted]
2. Name of organisation	British Oncology Pharmacy Association
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The purpose of BOPA, which is a registered charity, is to promote excellence in the pharmaceutical care of patients with cancer through education, communication, research and innovation by an alliance of hospital, community and academic pharmacists, pharmacy technicians, those in the pharmaceutical industry and other healthcare professionals. BOPA's principal objective is to promote excellence in the pharmaceutical care of patients with cancer, thereby improving their quality of life.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	Yes as sponsor for BOPA conference (ongoing). Non treatment related.

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	no

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Reduce the risk of recurrence/ cure
7. 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.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, node negative patients

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	EBC is normally treated with optimal hormonal manipulation, bisphosphonates (clinician decision based on predict or NPI score) and abemaciclib provided patient fits NHSE criteria (depending on disease characteristics)
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	ESMO, ASCO
9b. 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.)	It is well defined
9c. What impact would the technology have on the current pathway of care?	This treatment would be offered to more patients e.g. node negative breast cancer patients who meet specific criteria (grade 3 or grade 2 with Ki67 >20%, oncotype Dx recurrence score of 26 or high risk via other genomic profiling)
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	New line of therapy in the adjuvant setting
10a. How does healthcare resource use differ between the technology and current care?	
10b. In what clinical setting should the technology be used? (For example,	Specialist secondary care clinics (oncology)

primary or secondary care, specialist clinics.)	
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Training and staff numbers, ECG machines
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	yes
11a. Do you expect the technology to increase length of life more than current care?	yes
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	no

The use of the technology

13. 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 acceptability or ease of use or additional tests or monitoring needed.)	More difficult. More patients will be eligible for systemic anti-cancer therapy meaning more appointments needed with oncology team, more prescriptions processed by pharmacy and more time spent by nurses to review bloods.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Bloods, ECGs and patient reviews in clinic
15. 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?	Yes

16. 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?	Yes
16a. Is the technology a 'step-change' in the management of the condition?	Yes
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Neutropenia or hepatitis may mean deferral of treatment. More frequent appointments and bloods which can have more of an intrusive impact on patients' life ie. Taking time of work . This will be for 3 years rather than 2 with abemaciclib

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes

18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Disease free survival (90.4% with ribociclib and NSAI and 87.1% with NSAI alone)
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	no
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA810 and TA886]?	no
21. How do data on real-world experience	

compare with the trial data?	

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	no
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Ribociclib increases disease free survival compared to AI alone • In the trial it was available to a larger cohort patients compared to current practice (if compared to abemaciclib ie. Node negative patients)- grade 3 or grade 2 with Ki67 >20%, oncotype Dx recurrence score of 26 or high risk via other genomic profiling • Because of increase in the number of eligible patients, workload will increase on the cancer services workforce • Duration of treatment will be longer compared to abemaciclib 3 years versus 2 years, with appointments, bloods etc. will mean it will be more intrusive to patients lives compared to AI alone for example. • It will be an additional line of therapy in the adjuvant breast cancer setting

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ribociclib with an aromatase inhibitor for adjuvant treatment of hormone receptor-positive, HER2-negative early breast cancer [ID6153]

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.

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. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Clinical expert statement

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 **Wednesday 12 March 2025.** 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 hormone receptor-positive, HER2-negative early breast cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Prof David Cameron
2. Name of organisation	University of Edinburgh & NHS Lothian
3. Job title or position	Professor of Oncology
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 hormone receptor-positive, HER2-negative early breast cancer? ☒ A specialist in the clinical evidence base for hormone receptor-positive, HER2-negative early breast cancer 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.) Haven't seen it so cannot comment on what has been submitted to NICE
6. If you wrote the organisation submission and/or do not have anything to add, tick here.	☐ Yes

(If you tick this box, the rest of this form will be deleted after submission)	
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 hormone receptor-positive, HER2-negative early breast cancer ? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Cure of patients with early breast cancer, although a secondary benefit is to delay recurrence
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)	Statistically robust improvement in overall survival or distant recurrence free survival (as even in patients with recurrence, death may be delayed a long time and so improvement in Overall Survival may not yet be apparent). How much absolute improvement in recurrence or survival is a more complex question as it depends on the toxicity of therapy. Most clinicians would want at least a 3% absolute benefit fin 10 year overall survival for an individual patient to consider discussing chemotherapy with the patient, and a 5% gain to think chemotherapy is standard of care. For the addition of a CDK4/6inhibitor, there isnt yet a clinical consensus on the appropriate level of benefit, but in my cancer centre, we don't consider offering adjuvant CDK4/6inhibitors unless there is an estimated reduction in risk of distant recurrence of around 3-4%. Thus what is clinically a significant benefit depends on the absolute risk of the event which of course is different for different patients within the group for whom a treatment is approved!
10. In your view, is there an unmet need for patients and healthcare professionals in hormone receptor-positive, HER2-negative early breast cancer ?	YES – this group of patients contribute the most deaths from early breast cancer in the UK and therefore there is an unmet need whilst many of these patients still die from breast cancer
11. How hormone receptor-positive, HER2-negative early breast cancer currently treated in the NHS?	Many guidelines – national and regional a few links are included below https://www.nice.org.uk/guidance/ng101

• 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?	https://www.england.nhs.uk/mids-east/wp-content/uploads/sites/7/2018/02/guidelines-for-the-management-of-breast-cancer-v1.pdf https://ukbcg.org/guidelines/ patient focussing: https://breastcancernow.org/sites/default/files/best_treatment_guide_-_england_and_wales.pdf The core pathway and principles of treatment types and sequence are fairly standard although there are quite a few points where an individual clinician (and patient) may make different detailed choices. For example, choosing between breast conserving surgery and mastectomy; when to give and not give post-operative radiotherapy; when to give and not give adjuvant (or neo-adjuvant) chemotherapy and the choice of adjuvant (or neo-adjuvant) endocrine therapy. And finally when to give or not to give the current approved adjuvant CDK4/6i abemaciclib for 2 years, a treatment similar to the one (ribociclib) under consideration. The treatment (technology) under consideration could replace abemaciclib for some patients and be given to other patients still at significant risk of recurrence and death from breast cancer who do not meet the licensed indication for adjuvant abemaciclib. So it would in general be advantageous for patients to have access to ribociclib as an alternative CDK4/6i as well as the current access to abemaciclib.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes. After completion of surgery, radiotherapy (if given) and chemotherapy (if given), patients go onto long term (usually a minimum of 5 years and for higher risk patients up to 10 years) endocrine therapy. At present some of these patients – those at higher risk of recurrence and death from breast cancer and who meet the UK licence for abemaciclib, are offered this additional therapy

• 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)	given alongside their endocrine therapy for 2 years. Ribociclib if approved would "slot" into the care pathway at exactly the same point as abemaciclib does at present, and be used in place of abemaciclib for some patients and ALSO given to some other patients who don't currently get abemaciclib at the same point in the pathway. Both drugs (abemaciclib and ribociclib if approved) would be managed from secondary care with primary care often being asked in some parts of the NHS to take the necessary monitory blood tests. No new technology would be needed to introduce the drug as the NHS is already used to using the drug in advanced breast cancer, and to using abemaciclib in early breast cancer, but as its use is likely to increase the overall number of early breast cancer patients on adjuvant CDK4/6inhibitors, there would need to be a small expansion of current services, probably needing a mixture of additional Oncologists and Non-medical prescribers, and some of the latter will need extra training in the use of adjuvant CDK4/6 inhibitors.
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. For those patients who cannot tolerate adjuvant abemaciclib due to side effects, this would offer them an alternative way to get the additional benefit of delayed recurrence (and increased cure if longer follow-up confirms that this does improve overall survival) that they could have gained if they could have taken the abemaciclib. In addition there are other patients with similar significant risks of recurrence and death from breast cancer who cannot access abemaciclib under its current licence who could take (and benefit from) the use of ribociclib.2 years YES – for some patients who would otherwise develop recurrence and death from breast cancer, access to ribociclib would improve their long term quality of

	life, though of course like most medicines, in the short term there would be some loss of quality of life whilst on the therapy.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Good question. Unfortunately the design of most pharmaceutical company trials with little or no prospective primary translational research makes it hard to identify cases/cancers with higher or lower sensitivity to drugs. That is also the case with ribociclib – we don't know which cancers have a higher or lower chance of responding and the trial data suggests the relative benefit for a patients is the same (and thus only their absolute risk of recurrence/death changes their absolute benefit).
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 acceptability or ease of use or additional tests or monitoring needed)	For those who would take this as an alternative to adjuvant abemaciclib I would say it is overall neither easier nor more difficult – the toxicities are different and a few different safety checks are needed for ribociclib, but once a patient is established on either medicine the requirements are broadly similar, though of course ribociclib is taken for three years whereas abemaciclib is only taken for 2. For any patients who take ribociclib but who couldn't take abemaciclib under its current license, then there are extra tests, monitoring, hospital review etc, that wouldn't otherwise happen to those patients, so it is a little bit more work for them and the NHS. Ribociclib is given in this situation for 3 years whereas abemaciclib is given for only 2. However, importantly for service impact (as distinct from drug budget impact), almost all patients are on a stable dose well before year 3, and will likely be getting drug dispensed only every 12 weeks in the third and final year of therapy. Thus the final extra year of therapy with ribociclib will have marginal service impact as it will probably only involve 4 extra blood tests, and 4 extra clinic visits per patient, and usually not to a consultant oncologist, but in many hospitals a non-medical prescriber.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients will be monitored for side effects and laboratory blood effects. Drug dose may need to be altered in response to those symptoms and investigations. The SPC gives clear guidance on this and of course patient and clinician discretion will also play into it. And, in the unfortunate situation where a patient

	develops a recurrence of breast cancer whilst taking the therapy, it would normally be stopped (although if the recurrence was in fact a totally different new breast cancer primary then it probably would be continued).
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. In indirect comparison with abemaciclib, the urgency of the diarrhoea experienced by some patients on abemaciclib is probably not well picked up by QALY calculations (and of course direct comparison between the two technologies is not possible). So for those patients a switch to ribociclib (as is often done in the advanced disease setting) brings a QALY benefit that is hard to capture. Finally there is the aspect that whilst the additional benefits of chemotherapy and adjuvant CDK4/6 inhibitors are added, and head to head comparisons between chemotherapy and adjuvant CDK4/6inhibitors are so far few, there will be patients for whom chemotherapy is not really appropriate due to comorbidities but who could still tolerate CDK4/6inhibitors. Thus there are times when a clinician and patient choose the CDK4/6i rather than chemotherapy – and this differential QoL impact has NOT been assessed in the pivotal trials of either abemaciclib or ribocilcib and their trial design precluded this “either or” choice.
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?	NO – as the step change was made with the introduction of abemaciclih- what this offers is extension of the benefit to more patients (including those who cannot take abemaciclib even if they meet its license). YES _ it addresses the unmet need for those who cannot take abemaciclib for reasons of strict license or intolerability, yet have a sufficiently high risk early breast cancer that could benefit from the use of CDK4/6inhibitor 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?	Varies. Some patients have minimal side effects and so no impact on QoL other than having to attend hospital, have regular blood tests (which after a while may be only once every 12 weeks). Others will have more side effects with an impact on QoL. In my experience perhaps fatigue is the dominant one but is usually not severe though is persistent.
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? • 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?	YES although we don't know how many patients in the trial went on to get CDK4/6inhibitors after recurrence, as it was not available in all countries where the trial was run, but it would be expected to happen in the UK
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 [TA810]?	Yes – a preplanned additional analysis was published in 2024 (Rastogi et al J Clin Oncol 42:987-993) which confirms stability of the results of the Monarch E trial, including as yet no statistically significant impact on overall survival.
23. How do data on real-world experience compare with the trial data?	NONE available to my knowledge as this treatment indication has only been granted in the US about 1 year ago.
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	Not aware of any (in)equality issues with this technology that are different from those faced in general by breast cancer patients accessing treatments, nor from those patients eligible for the comparator drug abemaciclib specifically.

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 • 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.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

1) Introducing this indication into the NHS will not require a new service to be developed
2) For patients who could currently get adjuvant abemaciclib approving ribociclib will offer better patient choice which can be important in the face of tolerability problems, the impact of which may not have been well picked up in the QoL data of the pivotal trials
3) Introducing this indication will allow patients with high risk early breast cancer who don't meet the abemaciclib licence to also benefit from adjuvant CDK4/6inhibitors – so extending the benefit of this therapeutic approach to patients not currently able to benefit,
4) The three year duration of therapy is longer than the two years' of abemaciclib, but the vast majority of patients will be on a stable dose in their final year of therapy, and thus likely to be on a 12 week blood test and dispensation schedule, so only 4 extra blood tests and clinic visits (usually to a non-medical prescriber) for that extra year, so the additional service impact is small.

Click or tap here to enter text.

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.

NICE National Institute for Health and Care Excellence

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ribociclib with an aromatase inhibitor for adjuvant treatment of hormone receptor-positive, HER2-negative early breast cancer [ID6153]

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.

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. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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 **Wednesday 12 March 2025.** 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.

Part 1: Treating hormone receptor-positive, HER2-negative early breast cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Michal Sladkowski
2. Name of organisation	BOPA
3. Job title or position	Secretary of the Executive committee
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 hormone receptor-positive, HER2-negative early breast cancer? ☐ A specialist in the clinical evidence base for hormone receptor-positive, HER2-negative early breast cancer 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.	

8. What is the main aim of treatment for hormone receptor-positive, HER2-negative early breast cancer ? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
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)	
10. In your view, is there an unmet need for patients and healthcare professionals in hormone receptor-positive, HER2-negative early breast cancer ?	
11. How hormone receptor-positive, HER2-negative early breast cancer 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?	
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)	
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?	
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
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 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?	
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	
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?	
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?	
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? • 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?	
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA810]?	
23. How do data on real-world experience compare with the trial 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. 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.	

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.

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.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ribociclib with an aromatase inhibitor for adjuvant treatment of hormone receptor-positive, HER2-negative early breast cancer [ID6153]

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 hormone receptor-positive, HER2-negative early breast cancer or caring for a patient with hormone receptor-positive, HER2-negative early breast cancer. 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.

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. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Wednesday 12 March 2025.** 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, 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.

Patient expert statement

Ribociclib with an aromatase inhibitor for adjuvant treatment of hormone receptor-positive, HER2-negative early breast cancer [ID6153]

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with hormone receptor-positive, HER2-negative early breast cancer

Table 1 About you, hormone receptor-positive, HER2-negative early breast cancer, current treatments and equality

1. Your name	Eleanor Pearce Willis
2. Are you (please tick all that apply)	☐ A patient with hormone receptor-positive, HER2-negative early breast cancer ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with hormone receptor-positive, HER2-negative early breast cancer ☒ 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 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 hormone receptor-positive, HER2-negative early breast cancer? **If you are a carer (for someone with hormone receptor-positive, HER2-negative early breast cancer) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for hormone receptor-positive, HER2-negative early breast cancer 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 hormone receptor-positive, HER2-negative early breast cancer (for example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of ribociclib with an aromatase inhibitor 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 ribociclib with an aromatase inhibitor 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 ribociclib with an aromatase inhibitor over current treatments on the NHS please describe these. For example, are there any risks with ribociclib with an aromatase inhibitor? 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 ribociclib with an aromatase inhibitor 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 hormone receptor-positive, HER2-negative early breast cancer and ribociclib with an aromatase inhibitor? 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?	

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.

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.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ribociclib with an aromatase inhibitor for adjuvant treatment of hormone receptor-positive, HER2-negative early breast cancer [ID6153]

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 hormone receptor-positive, HER2-negative early breast cancer or caring for a patient with hormone receptor-positive, HER2-negative early breast cancer. 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.

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. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Wednesday 12 March 2025.** 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, 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.

Patient expert statement

Ribociclib with an aromatase inhibitor for adjuvant treatment of hormone receptor-positive, HER2-negative early breast cancer [ID6153]

Part 1: Living with this condition or caring for a patient with hormone receptor-positive, HER2-negative early breast cancer

Table 1 About you, hormone receptor-positive, HER2-negative early breast cancer, current treatments and equality

1. Your name	Kirstin Spencer
2. Are you (please tick all that apply)	☒ A patient with hormone receptor-positive, HER2-negative early breast cancer ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with hormone receptor-positive, HER2-negative early breast cancer ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Independent Cancer Patient's Voice (ICPV)
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 submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing

Patient expert statement

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: Other patients through forums and Charities, ☒ 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 hormone receptor-positive, HER2-negative early breast cancer? **If you are a carer (for someone with hormone receptor-positive, HER2-negative early breast cancer) please share your experience of caring for them**	**6.** Recurrence and/or metastatic disease was a huge concern for me and it is for other patients with early breast cancer. It is very difficult trying to live with not knowing if you are going to go on to get recurrent or a metastatic terminal disease. The treatments for hormone receptor positive breast cancer can feel brutal with surgery often being the mainstay of treatment followed by an array of challenging treatments. After initial diagnosis and treatment it can be **difficult to access any meaningful follow up.** Primary breast cancer patients can be **left distressed** as requests for follow up and surveillance for recurrent disease can be refused depending on where they live and their Doctor. There is a **paucity of data** to really understand the patient numbers succumbing to recurrent disease and/or secondary metastatic disease. The majority of metastatic breast cancer patients progress from primary breast cancer. The 'unknown' of who

	is going to progress adds to the concern of primary breast cancer patients. They can be left wondering… "**Could it be you?**". **Primary Breast Cancer patient voice:** *"I'm **feeling so overwhelmed and upset** about chemo. I'm concerned about reoccurrence and will life ever be the same again…"* *"**I was given an MRI** every year for 5 years… if you have dense breasts… ask for MRI's"* *"I have asked for an MRI because of dense breasts and was told '**you don't need one**'. How am I going to be monitored?"* *"**A local recurrence missed or ignored becomes a terminal disease**…"* *"It's so completely unfair - **I was offered MRI** annually until I'm 50 without question but so many others seem not to be given this option".* *"They **refused to give me MRI's** for surveillance…"* *"I hear that 30% of primary breast cancer patients will become metastatic. How will they know if I am?"*

	*"The **worry of reoccurrence is big** & very real"* *"Just the word 'chemo' puts the fear of God into you".* *"I thought I was coping well… I ended up in hospital with heart problems"* *"I feel my **future has been stolen**"* *"**That fear of reoccurrence never truly leaves any of us**"*
7a. What do you think of the current treatments and care available for hormone receptor-positive, HER2-negative early breast cancer on the NHS?	**7a.** Current treatments available on the NHS for early breast cancer offer a strong opportunity to subdue the disease. However, as we understand more about breast cancer and the enormous heterogeneity of this disease, a one-size fits all approach can be hazardous and we need options within the policies and guidelines to reflect this. Decisions of doctors need to be aligned as closely as possible to the actual disease presenting itself within each early breast cancer patient in clinic. Over treatment needs to be avoided for toxicity reasons but the side-effect of undertreatment may lead to the terminal disease of metastatic breast cancer. I personally have concerns about using Abemaciclib in an adjuvant setting. It may potentially restrict patient options later on should they progress to a metastatic disease.

7b. How do your views on these current treatments compare to those of other people that you may be aware of?	**7b.** Generally many **women** who have had primary breast cancer have said they are **fearful** of **disease recurrence** and question whether they are receiving optimal treatment for their disease. This has been my biggest concern too. There seems to be some inequity of patients accessing optimal treatment amongst hospitals in the U.K. Internet forums can be very strong and patients can connect, discuss and compare treatments. Too often **effective treatment may depend on the knowledge and tenacity of the individual Doctor and/or the patient**. Women are feeling they have to become **'experts' of their own disease** which is a cruel reality to face after just having received a diagnosis of breast cancer and not always possible for women who are already juggling families and work. Some cohorts of patients such as those who have multi-focal disease or a less common breast cancer type (e.g. lobular breast cancer) fear they are not treated optimally because they miss fitting into 'narrowly set' criteria and may struggle to access drugs if tumours are only measured in largest size rather than adding up quantity of them all and trials which may insist on fulfilling a narrow criteria to be accepted. **Primary Breast Cancer patient voice:**

	"*I am stage 2b with 3 lymph nodes… like many with lobular I had 5 tumours, smallest being 30mm, but total tumour burden 95mm. I worry that* ***stage 2b doesn't fully reflect my situation but I didn't qualify for abemaciclib****".* *"I have stage 2 lobular and started Ribociclib in October 2024 – **I am so grateful to be able to access this drug**…"* *"I'd take it (Ribociclib) if appropriate, I was one node away from being offered Abemaciclib…"* "*I was on Ribociclib full dose, ALT went up and down (including when I stopped it). Liver scan was fine… put on palbociclib instead, started on middle dose and reduced to lowest… Same problem with ALT. Now on Abemaciclib at lowest dose. So far so good…"*
8. If there are disadvantages for patients of current NHS treatments for hormone receptor-positive, HER2-negative early breast cancer (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Currently the only CDK 4/6 inhibitor offered for early breast cancer is Abemaciclib with either an Aromatase Inhibitor (AI) or other antioestrogen treatment and fulfilling specific high risk criteria. The NICE recommendation of the Abemaciclib followed from the results of the MonarchE trial which selected patients with HR+, HER2- Early Breast Cancer (EBC) at high risk of recurrence. Access to that drug combination depended on the patient having met criteria of having; • four or more positive armpit nodes or

	• 1-3 nodes and…
	  ○ a primary tumour greater than or equal to 5cm,
	  ○ Grade III disease (defined as at least 8 points on the modified Bloom-Richardson grading system or equivalent).
	
	NICE recommends olaparib (alone or with endocrine therapy), for the adjuvant treatment of HER2 negative early breast cancer with germline BRCA1 or 2 mutations following chemotherapy. Olaparib has been available on the NHS in England and Wales for women with early-stage, high-risk breast cancer with inherited mutations in BRCA1 or BRCA2 since April 2023 following results from the OlympiA trial. This has enabled patients to have a targeted treatment for their mutation after chemotherapy and surgery. Despite NATALEE reporting positive results for ribociclib, recent guidelines suggest if an early germline BRCA breast cancer patient is eligible for both olaparib and ribociclib, olaparib should be given first (Loibl *et al.,* 2024).
	
	Disadvantages;
	• Patient population has to meet the above criteria to access abemaciclib and some patients are left feeling **undertreated** as they would not be able to access olaparib either if they did not have a BRCA mutation and no nodal involvement (it is difficult for medical teams to know who is going to recur).
	• The toxicity profile of abemaciclib, the only CDK 4/6 inhibitor currently offered to high risk of recurrence early breast cancer patients is not suited to all patients and an **alternative pathway is much needed**.

Patient expert statement

	• Using Abemaciclib in the adjuvant setting **may limit patient options later** on. Ribociclib may offer an alternative. • Aromatase Inhibitor use can lead to ESR1 mutations driving resistance to CDK 4/6 inhibition (and I wonder why fulvestrant is not used more frequently in the adjuvant setting). • Quantity of **multi-focal tumours continue to be dismissed** with only the largest one counted **References;** Loibl, S. et al. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann. Oncol.35, 159–182 (2024).
9a. If there are advantages of ribociclib with an aromatase inhibitor 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?	**9a.** Ribociclib has had positive results for ER+ HER2- disease when compared to treating it with an aromatase inhibitor alone. **Advantages;** • A broader population of patients are able to access Ribociclib (node **negative and** node **positive** patients were accepted by this trial, so was **Stage II in addition to Stage III disease**). • **Reduced dose** of Ribociclib (400mg) may **reduce drug toxicities**. The trial saw a lower incidence of neutropenia (low white blood cell count) and QT prolongation (delays in the heart's electrical system as it takes longer to contract and relax), hence no tamoxifen to be used with it. (Patients should still be warned about Interstitial Lung disease.)

	• Lower dose of Ribociclib may also **support treatment adherence by patient.** • An **absolute benefit** with ribociclib plus an non-steroidal aromatase inhibitor (NSAI) over an NSAI alone at 3 years was **3.1%.** (Hortobagyi *et al.,* 2025)
9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?	**9b.** The most important advantage to patients will likely be offering the CDK 4/6 inhibitor treatment to a **broader patient population**. This is because we don't yet know who will get recurrent disease and why. Access to Ribociclib may enable more patients the hope to 'dodge or delay' recurrent and/or metastatic disease.
9c. Does ribociclib with an aromatase inhibitor 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	**9c.** Yes**;** • It is difficult to know - given the complexity and heterogeneity of breast cancer, including number of subtypes and monitoring challenges, especially in the adjuvant setting, who is and who is not going to suffer recurrent disease. Allowing a wider cohort of patients access to this drug may help **prevent/delay recurrence** and/or distant metastasis. • Toxicity profiles differ between the CDK 4/6 inhibitors and patients may find they tolerate one drug over the other. **It is better to have options.** • Patients and their Doctors may prefer to use Ribociclib in the adjuvant setting so (potentially) they may still able to access Abemaciclib later on should they need. Considering scientists are of the opinion that **HR+ breast cancer** has a **lifelong chance of recurrence**, this point may be worth deliberation.

	• Current treatment offers Abemaciclib to a very specific cohort of high risk patients. **Primary Breast Cancer patient voice:** *"I believe we should have access to all 3 CDK 4/6 inhibitors as many struggle with Abemaciclib and it would be wonderful to have another alternative"* *"…it would depend on the side effects."* *"I would have liked this (Ribociclib)… my tumour was 43mm – for Abemaciclib it has to be minimum 5cm – I had a further 2 ops to get clear margins taking more but has to be initial tumour."* *"I would absolutely go for it if it reduces the risk of recurrence".* **Reference;** Hortobagyi, G.N., Lacko, A., Sohn, J., Cruz, F., Ruiz Borrego, M., Manikhas, A., Hee Park, Y., Stroyakovskiy, D., Yardley, D.A., Huang, C.-S., Fasching, P.A., Crown, J., Bardia, A., Chia, S., Im, S.-A., Martin, M., Loi, S., Xu, B., Hurvitz, S., Barrios, C., Untch, M., Moroose, R., Visco, F., Parnizari, F., Zarate, J.P., Li, Z., Waters, S,. Chakravartty, S., Slamon, D. '*A phase III trial of adjuvant ribociclib plus endocrine therapy versus endocrine therapy alone in patients with HR-positive/HER2-negative early breast cancer: final invasive disease-free survival results from the NATALEE trial*', Annals of Oncology, Volume 36, Issue 2, 2025. Pages 149-157, ISSN 0923-7534, https://doi.org/10.1016/j.annonc.2024.10.015.

10. If there are disadvantages of ribociclib with an aromatase inhibitor over current treatments on the NHS please describe these. For example, are there any risks with ribociclib with an aromatase inhibitor? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Ribociclib does have some reported side effects. However, these are not mandatory and some patients report no side effects at all or manageable ones. Many cancer drugs do have side effects and these can differ depending on the individual patient. The lowered dose suggested for adjuvant setting may help reduce any toxicities. **Primary Breast Cancer patient voice:** "*I am so grateful to be able to access to this drug & no side effects for me…"* (on Ribociclib for 6 months)
11. Are there any groups of patients who might benefit more from ribociclib with an aromatase inhibitor 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	**Benefit more;** • People with more aggressive stage II early breast cancers or those who fall outside the remit of abemaciclib and olaparib. **Benefit less;** • Patients with early ESR1 mutations because ESR1 mutations (specifically most common D538G and Y537S) are found to drive resistance both in real world and pre-clinical evidence to CDK 4/6 inhibitors. (Lin *et al.,* 2025) • Patients who find Ribociclib a difficult drug to tolerate and suffer metabolically or otherwise • BRCA 1 and 2 patients may prefer the PARP inhibitor Olaparib which specifically targets their mutation as Dubsky *et al.,* (2023) suggest inferior outcomes using CDK 4/6 inhibition or endocrine therapy for germline BRCA

	mutated patients in comparison to patients without germline BRCA mutations. **Reference;** Dubsky, P., Jackisch, C., Im, SA. *et al.* BRCA genetic testing and counselling in breast cancer: how do we meet our patients' needs?. *npj Breast Cancer* **10**, 77 (2024). https://doi.org/10.1038/s41523-024-00686-8 Lin CA, Chica-Parrado MR, Unni N, Jaeger E, Fang YV, Guo L, Napolitano F, Luna P, Harris M, Chao C, Xu L, Arteaga CL, Hanker AB. *'ESR1 Y537S and D538G mutations drive resistance to CDK4/6 inhibitors in estrogen receptor-positive breast cancer*.' Clin Cancer Res. 2025 Feb 25. doi: 10.1158/1078-0432.CCR-24-2307. Epub ahead of print. PMID: 39992682
12. Are there any potential equality issues that should be taken into account when considering hormone receptor-positive, HER2-negative early breast cancer and ribociclib with an aromatase inhibitor? 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	None were noted.

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?	Data immaturity for setting in EBC patients. Will eligible patients who experience toxicity on either CDK 4/6 inhibitor be allowed to swap?

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- **Broader population** of patients able to access the drug who **currently feel undertreated** and those with multi-focal tumours where currently only the largest of the tumours is counted. (Node **negative and** node **positive** patients were accepted by the NATALEE trial, so was **Stage II in addition to Stage III disease**).
- Reduced dose of Ribociclib (400mg) for the patient may reduce toxicity and support patient adherence.
- An **absolute benefit** with ribociclib plus an NSAI over an NSAI alone at 3 years was **3.1%.** (Hortobagyi *et al.,* 2025)
- An alternative option for patients and their Doctors who may qualify for Abemaciclib and Olaparib but (for whatever reason) cannot take these drugs.

Thank you for your time.

Patient expert statement

NICE National Institute for Health and Care Excellence

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

EAG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Ribociclib with an aromatase inhibitor for adjuvant treatment of hormone receptor-positive, HER2-negative early breast cancer [ID6153]

Confidential until published

This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR136255

Completed 20 January 2025 (updated 13 February 2025)

CONTAINS [redacted] DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Ribociclib with an aromatase inhibitor for adjuvant treatment of hormone receptor-positive, HER2-negative early breast cancer [ID6153]

Produced by: Liverpool Reviews & Implementation Group (LR*i*G)

Authors: Rebecca Bresnahan, Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Rebecca Harvey, Director, Cabourn Statistics Ltd, Warrington

Angela Stainthorpe, Deputy Director, LR*i*G, University of Liverpool

Sophie Beale, Director, HARE Research, North Yorkshire

Angela Boland, Director, LR*i*G, University of Liverpool

Yenal Dundar, Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Joanne McEntee, Senior Medicines Information Pharmacist, North West Medicines Information Centre, Liverpool

Zafar Malik, Consultant Clinical Oncologist. The Clatterbridge Cancer Centre, Liverpool

Correspondence to: Rebecca Bresnahan, Research Fellow, Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB

Date completed: 20 January 2025 (updated 13 February 2025)

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR 136255.

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.

Declared competing interests of the authors: None to declare.

This report should be referenced as follows: Bresnahan R, Harvey R, Stainthorpe A, Bryning S, Beale S, Boland A, Dundar Y, McEntee J, Malik Z. Ribociclib with an aromatase inhibitor for adjuvant treatment of hormone receptor-positive, HER2-negative early breast cancer [ID6153]: A Single Technology Appraisal. LRiG, University of Liverpool, 2025.

Contributions of authors:

Rebecca Bresnahan	Project lead, critical appraisal of the clinical evidence and supervised production of the final report
Rebecca Harvey	Critical appraisal of the statistical evidence
Angela Stainthorpe	Critical appraisal of the economic evidence
Sophie Beale	Critical appraisal of the evidence, editorial input
Angela Boland	Critical appraisal of the evidence, editorial input
Yenal Dundar	Critical appraisal of the search strategies
Joanne McEntee	Critical appraisal of the company submission
Zafar Malik	Clinical advice and critical appraisal of the clinical evidence

Table of contents

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
AI	aromatase inhibitor
AIC	Akaike information criterion
ALT	alanine transaminase
BIC	Bayesian information criterion
BRCA	BReast CAncer gene
CDK	cyclin-dependent kinase
CRD	Centre for Reviews and Dissemination
CS	company submission
CSR	clinical study report
DDFS	distant disease-free survival
DR	distant recurrence
DRFS	distant relapse-free survival
EAG	Evidence Assessment Group
EORTC QLQ-BR23	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire breast cancer module
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core
EQ-5D-5L	EuroQol-5 Dimensions-5 Levels
ER	oestrogen receptor
ESS	effective sample size
ET	endocrine therapy
GnRH	gonadotropin hormone-releasing hormone
HADS	Hospital Anxiety And Depression Scale
HER2-negative	human epidermal growth factor receptor 2-negative
HR	hazard ratio
HR-positive	hormone receptor-positive
HRQoL	health-related quality of life
HTA	Health Technology Assessment
IA	interim analysis
ICER	incremental cost-effectiveness ratio
iDFS	invasive disease-free survival
IPD	individual patient data
ITC	indirect treatment comparison
ITT	intention-to-treat
K-M	Kaplan-Meier
MAIC	matching-adjusted indirect comparison
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NMR	non-metastatic recurrence
OS	overall survival

PA	primary pre-planned analysis
PAS	Patient Access Scheme
PFS	progression-free survival
PH	proportional hazards
PRO	patient-reported outcome
QALY	quality adjusted life year
QD	once daily
RCT	randomised controlled trial
RDI	relative dose intensity
RFS	recurrence-free survival
SLR	systematic literature review
SPM	second primary malignancy
STC	simulated treatment comparison
TEAE	treatment-emergent adverse event
TSAP	trial statistical analysis plan
TTD	time to treatment discontinuation
TTE	time-to-event

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.

Section 1.1 provides an overview of the key issues identified by the EAG. Section 1.2 provides an overview of key modelling assumptions that have the greatest effect on the incremental cost effectiveness ratio (ICER) per quality adjusted life year (QALY) gained. Sections 1.3 to 1.6 explain the key issues identified by the EAG in more detail. Key cost effectiveness results are presented in Section 1.6.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table A Summary of the EAG's key issues

Issue	Summary of issue	Report sections
Issue 1	NATALEE trial populations and relevant comparators	2.4.2, 2.4.4, 3.7
Issue 2	Generalisability of the NATALEE trial AI arm to NHS patients treated with ET	2.3, 2.4.4, 3.2.3
Issue 3	Is DDFS a more appropriate proxy for OS than iDFS?	2.4.5
Issue 4	Mislabelled company MAIC: ribociclib+AI versus ET (Population 4)	2.4.4, 3.2.2, 3.4, 3.4.7, 3.7.2, 5.1
Issue 5	Company OS STC and OS MAIC results are not consistent (Population 4, ribociclib+AI versus abemaciclib+ET)	3.4.5, 3.4.6, 3.4.7, 3.7.2
Issue 6	Overall survival generated by the cost effectiveness model	6.1
Issue 7	Cost effectiveness results for patients ineligible for treatment with abemaciclib+ET	6.2
Issue 8	iDFS treatment effect waning	6.3.3
Issue 9	iDFS survival modelling	6.3.1
Issue 10	iDFS event distribution	6.3.1
Issue 11	ET-resistant and ET-sensitive DR substate: PFS and OS	6.4
Issue 12	ET-resistant and ET-sensitive DR substate: treatment mix	6.4
Issue 13	ET-resistant and ET-sensitive DR substate: utility values	6.4.4

AI=aromatase inhibitor; ET=endocrine therapy; iDFS=invasive disease-free survival; ITT=intention-to-treat; MAIC=matching-adjusted indirect comparison; NHS=National Health Service; OS=overall survival; PFS=progression-free survival; STC=simulated treatment comparison

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a QALY. An ICER per QALY gained is the ratio of the extra cost for every QALY gained.

The EAG highlights that OS over time (including median OS) cannot be directly estimated from the model due to the payoff approach used to estimate life years in the DR health state and because deaths due to second primary malignancies were not included. Until model OS estimates can be compared with clinician and published estimates, company and EAG cost effectiveness results may not be robust. This issue is of particular concern for the comparisons of ribociclib+AI versus ET as, for the comparison of ribociclib+AI versus abemaciclib+ET, the company survival estimates for patients treated with these two treatments are almost identical.

The EAG has revised the company model by:

- adjusting the invasive disease-free survival (iDFS) distribution
- choosing alternative progression-free survival (PFS) and overall survival (OS) in the distant recurrence (DR) health state
- adjusting treatment mix in endocrine therapy (ET)-resistant DR substate
- adjusting treatment mix in ET-sensitive DR substate
- changing ET-sensitive health state utility values
- adjusting adverse event (AE) unit costs
- investigating the impact of adjusting iDFS treatment effect waning assumptions

1.3 The decision problem: summary of the EAG's key issues

Issue 1 NATALEE trial populations and relevant comparators

Report section	2.4.2, 2.4.4, 3.7
Description of issue and why the EAG has identified it as important	The NATALEE trial ITT population (Population 1) is in line with the anticipated UK licensed indication for ribociclib+AI. However, the NATALEE trial ITT population (Population 1) includes patients who would be eligible for abemaciclib+ET (Population 4; TA810) and patients who would not be eligible for abemaciclib+ET (Population 5). Population 5 clinical (and cost) effectiveness evidence was not provided in the CS. Focusing on the NATALEE trial ITT population is problematic as the trial comparator is AI; most NHS patients who are eligible for treatment with abemaciclib+ET would be treated with abemaciclib+ET, not ET. Eligibility for abemaciclib+ET was not a NATALEE trial pre-specified outcome.
What alternative approach has the EAG suggested?	In response to clarification question A2, the company provided clinical effectiveness evidence for Population 5.
What is the expected effect on the cost effectiveness estimates?	See Issue 7.
What additional evidence or analyses might help to resolve this key issue?	See Issue 7.

AI=aromatase inhibitor; CS=company submission; EAG=External Assessment Group; ET=endocrine therapy; ITT=intention-to-treat; NHS=National Health Service

Issue 2 Generalisability of the NATALEE trial AI arm data to NHS patients treated with ET

Report section	2.3, 2.4.4, 3.2.3
Description of issue and why the EAG has identified it as important	Clinical advice to the EAG is that, in NHS clinical practice, ET can include: anastrozole, letrozole, exemestane and tamoxifen (and ovarian suppression). In the NATALEE trial, the only permitted ETs were the AIs, anastrozole and letrozole (investigators' choice). Clinical advice to the EAG is that this was reasonable because most NHS patients receive either anastrozole or letrozole. However, clinical advice to the company is that [redacted] of patients receive letrozole, [redacted] receive anastrozole and the remainder are likely to receive exemestane ([redacted]) or tamoxifen ([redacted]).
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost effectiveness estimates?	Not known.
What additional evidence or analyses might help to resolve this key issue?	Seek further clinical advice on whether NATALEE trial AI results can be generalised to NHS patients treated with ET. See Issue 4.

AI=aromatase inhibitor; EAG=External Assessment Group; ET=endocrine therapy; NHS=National Health Service

Issue 3 Is DDFS a more appropriate proxy for OS than iDFS?

Report section	2.4.5
Description of issue and why the EAG has identified it as important	The NATALEE trial primary endpoint is iDFS. The company stated that "iDFS is considered a clinically meaningful surrogate endpoint for OS, as disease recurrence is associated with breast cancer mortality" and that "observed improvements in these endpoints [iDFS and DDFS] are anticipated, in the long-term, to translate into improvements in OS". Clinical advice to the EAG is that DDFS is a more appropriate proxy for OS than iDFS.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost effectiveness estimates?	Not known.
What additional evidence or analyses might help to resolve this key issue?	Seek further clinical opihfnion on the most relevant proxy for OS.

DDFS=distant disease-free survival; EAG=External Assessment Group; iDFS=invasive disease-free survival; OS=overall survival

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 4 Mislabelled company MAIC: ribociclib+AI versus ET (Population 4)

Report section	2.4.4, 3.2.2, 3.4, 3.4.7, 3.7.2, 5.1
Description of issue and why the EAG has identified it as important	The EAG considers that the company comparative efficacy results presented for ribociclib+AI versus ET are not strictly based on an indirect comparison; rather, a re-weighted IPD analysis has been performed. This analysis has been informed by NATALEE trial outcome data only (despite matching to summary patient characteristics from the monarchE trial). Comparative efficacy is therefore based on an analysis of weighted NATALEE trial Population 4 ribociclib+AI and AI IPD.
What alternative approach has the EAG suggested?	None. For clarity, the EAG has used the term reweighted IPD analysis for the comparison of ribociclib+AI versus ET (Population 4).
What is the expected effect on the cost effectiveness estimates?	NA
What additional evidence or analyses might help to resolve this key issue?	Seek further clinical opinion on whether NATALEE trial AI or monarchE trial ET is most representative of ET in NHS clinical practice. If clinical advice to the NICE AC does not agree with the company that the permitted ETs in the NATALEE trial AI arm (letrozole and anastrozole) are more representative of ET in NHS clinical practice than the permitted ETs in the monarchE trial ET arm (tamoxifen, toremifene, letrozole anastrozole and exemestane), then STC analyses for the comparison of ribociclib vs ET are required.

AI=aromatase inhibitor; EAG=External Assessment Group; ET=endocrine therapy; IPD=individual patient data; NA=not applicable; NICE AC=National Institute for Health and Care Excellence Appraisal Committee; STC=simulated treatment comparison

Issue 5 Company OS STC and OS MAIC results are not consistent (Population 4, ribociclib+AI versus abemaciclib+ET)

Report section	3.4.5, 3.4.6, 3.4.7, 3.7.2
Description of issue and why the EAG has identified it as important	Due to concerns about the substantial reduction in the post-weighted ESS in the company MAICs, the EAG asked the company to carry out STCs for the comparison of ribociclib+AI versus abemaciclib+ET (Population 4). The EAG notes that the OS STC result is [redacted] whereas the OS MAIC results are [redacted]. The company OS STC result is based on an adjustment factor obtained from fitting a Weibull model to the NATALEE trial IPD; the EAG recognises that this result may be sensitive to the choice of parametric distribution.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Perform STCs based on an adjustment factor obtained from fitting alternative models to the NATALEE trial IPD data to explore whether the result is sensitive to the choice of parametric distribution

AI=aromatase inhibitor; EAG=External Assessment Group; ET=endocrine therapy; IPD=individual patient data; MAIC=matching-adjusted indirect comparison; OS=overall survival; STC=simulated treatment comparison

1.5 The cost effectiveness evidence: summary of the EAG's key issues

Issue 6 Overall survival generated by the cost effectiveness model

Report section	6.1
Description of issue and why the EAG has identified it as important	OS over time (including median OS) cannot be directly estimated from the model as a payoff approach was used to calculate life years in the DR health state and because deaths due to second primary malignancies were not included. The EAG has not been able to validate underlying OS informing cost effectiveness results. Therefore, all model cost effectiveness results may not be robust. This issue is of particular concern for the comparison of ribociclib+AI versus ET. For the comparison of ribociclib+AI versus abemaciclib+ET, the company survival estimates for patients treated with these two treatments are almost identical.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	None.

AI=aromatase inhibitor; DR=distant recurrence; EAG=External Assessment Group; ET=endocrine therapy; OS=overall survival

Issue 7 Cost effectiveness results for patients ineligible for treatment with abemaciclib+ET

Report section	6.2
Description of issue and why the EAG has identified it as important	The company has not presented Population 5 (only patients ineligible for abemaciclib+ET) cost effectiveness results; therefore, the EAG Population 5 cost effectiveness results have been generated using Population 1 data. The company stated that "the efficacy of ribociclib+AI versus ET in [the NATALEE high-risk ineligible for the abemaciclib] population is aligned with that of the broader ITT population". However, the EAG considers that NATALEE trial iDFS results for ribociclib+AI versus AI are slightly more favourable for Population 5 than for Population 1.
What alternative approach has the EAG suggested?	The EAG has assumed that Population 1 data can be used as a proxy for Population 5 data.
What is the expected effect on the cost effectiveness estimates?	Using Population 1 data to generate ICERs per QALY gained for Population 5 may be a conservative approach.
What additional evidence or analyses might help to resolve this key issue?	Ask the company to generate cost effectiveness results for Population 5 using Population 5 clinical effectiveness data.

AI=aromatase inhibitor; EAG=External Assessment Group; ET=endocrine therapy; ICER=incremental cost effectiveness ratio; iDFS=incremental disease free survival; QALY=quality adjusted life year

Issue 8 iDFS treatment effect waning

Report section	6.3.3
Description of issue and why the EAG has identified it as important	The EAG considers that the company iDFS treatment effect waning assumption is arbitrary, highly uncertain and not supported by evidence. Varying the treatment waning assumption has a substantial impact on cost effectiveness results for the comparison of ribociclib+AI versus ET.
What alternative approach has the EAG suggested?	The EAG has presented scenarios where treatment effect waning occurs more quickly than in the company base case and where treatment effect waning has been removed entirely.
What is the expected effect on the cost effectiveness estimates?	For Population 1 (ribociclib+AI versus ET), adjusting the treatment effect waning assumption results in deterministic ICERs per QALY gained that range from £9,263 to £32,204, once all the EAG revisions are in place. For Population 4 (ribociclib+AI versus ET), adjusting the treatment effect waning assumption results in deterministic ICERs per QALY gained ranging from £5,380 to £23,584, once all the EAG revisions are in place.
What additional evidence or analyses might help to resolve this key issue?	None.

AI=aromatase inhibitor; EAG=External Assessment Group; ET=endocrine therapy; ICER=incremental cost effectiveness ratio; iDFS=incremental disease free survival; QALY=quality adjusted life year

Issue 9 iDFS survival modelling

Report section	6.3.1
Description of issue and why the EAG has identified it as important	NATALEE trial iDFS data are immature and long-term iDFS estimates are subject to substantial uncertainty. Published iDFS data are only available to validate company extrapolations up to 10 years and the long-term iDFS estimates from company fitted curves vary considerably beyond 10 years.
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Seek clinical advice on iDFS beyond 10 years for patients with HR positive/HER2 negative early breast cancer at high risk of recurrence.

EAG=External Assessment Group; HR=hormone receptor positive; HER2=human epidermal growth factor receptor 2 iDFS=incremental disease-free survival

Issue 10 iDFS event distribution

Report section	6.3.1
Description of issue and why the EAG has identified it as important	The company has assumed that the proportions of iDFS events that are death, SPM, NMR or DR differ according to treatment but are the same for Population 1 and Population 4. For each health state, the 95% CIs for each treatment overlap substantially, indicating that there is insufficient statistical evidence of a difference between the iDFS event distributions based on treatment.
What alternative approach has the EAG suggested?	Ribociclib+AI iDFS event distributions used for all treatments.
What is the expected effect on the cost effectiveness estimates?	For Population 1, the EAG revision increased the ICER per QALY gained to £2,800. For Population 4, the EAG revision had no impact on the cost effectiveness of ribociclib+AI versus abemaciclib+ET; and for the comparison of ribociclib+AI versus ET, the ICER per QALY gained remained dominant.
What additional evidence or analyses might help to resolve this key issue?	Ask the company to undertake a pooled analysis of iDFS events across treatments and present updated cost effectiveness results (as appropriate).

AI=aromatase inhibitor; CI=confidence interval; DR=distant recurrence; EAG=External Assessment Group; ET=endocrine therapy; ICER=incremental cost effectiveness ratio; iDFS=incremental disease-free survival; NMR=non-metastatic recurrence; QALY=quality adjusted life year; SPM=second primary malignancy

Issue 11 ET-resistant and ET-sensitive DR substate: PFS and OS

Report section	6.4
Description of issue and why the EAG has identified it as important	The EAG has two concerns about the company's base case approach to modelling PFS and OS for subsequent treatments in the ET-resistant and ET-sensitive substates: it is not appropriate to apply HRs to loglogistic (OS) and lognormal (PFS) curves, and the long-term PH assumptions have not been justified for the comparison of ribociclib+AI versus the baskets of treatments. These two issues impact the costs and QALYs generated in the DR health state.
What alternative approach has the EAG suggested?	For ribociclib+AI in the ET-sensitive DR substate, the EAG has used the company post-progression efficacy scenario PFS (exponential) and OS (Gamma) curves. For ribociclib+AI in the ET-resistant DR substate, the EAG has used the exponential curve for PFS and the company post-progression efficacy scenario OS (Weibull) curve. The EAG has not made any changes to the HRs used by the company to generate PFS and OS curves for non-ribociclib treatments.
What is the expected effect on the cost effectiveness estimates?	For Population 1, the EAG revision increased the ICER per QALY gained to £967. For Population 4, the EAG revision had no effect on cost effectiveness results, i.e., ribociclib+AI dominated abemaciclib+ET and dominated ET.
What additional evidence or analyses might help to resolve this key issue?	Seek clinical advice to validate long-term PFS and OS in ET-resistant and ET-sensitive patients.

AI=aromatase inhibitor; DR=distant recurrence; EAG=External Assessment Group; ET=endocrine therapy; ICER=incremental cost effectiveness ratio; PFS=progression-free survival; QALY=quality adjusted life year; OS=overall survival

Issue 12 ET-resistant and ET-sensitive DR substate: treatment mix

Report section	6.4
Description of issue and why the EAG has identified it as important	The proportion of ET-resistant and ET-sensitive patients who had been previously treated with a CDK4/6 inhibitor (ribociclib or abemaciclib) who are likely to receive a subsequent CDK4/6 inhibitor is uncertain. However, the company base case proportions are not in line with clinical advice to the company.
What alternative approach has the EAG suggested?	The EAG has revised the proportions of treatments received in the ET-resistant and ET-sensitive DR substates to reflect clinical advice to the company.
What is the expected effect on the cost effectiveness estimates?	For Population 1, the EAG revision increased the ICERs per QALY gained versus ET to £3,116 (ET-resistant) and £2,205 (ET-sensitive). For Population 4, the EAG revision had no effect on cost effectiveness results, i.e., ribociclib+AI dominated abemaciclib+ET and dominated ET.
What additional evidence or analyses might help to resolve this key issue?	None expected, as real world evidence to inform treatment patterns is unlikely to be available in the short term.

AI=aromatase inhibitor; DR=distant recurrence; EAG=External Assessment Group; ET=endocrine therapy; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year

Issue 13 ET-resistant and ET-sensitive DR substate: utility values

Report section	6.4.4
Description of issue and why the EAG has identified it as important	The modelled progression-free utility values are the same for both the ET-resistant DR substate and the ET-sensitive DR substate, but ET-resistant disease is often more aggressive than ET-sensitive disease and would therefore be expected to be associated with lower HRQoL.
What alternative approach has the EAG suggested?	The EAG revision has replaced the ET-sensitive progression free utility value with the NMR health state utility value and estimated progressed disease utility values by calculating the ratio of progressed disease to progression free disease utility values.
What is the expected effect on the cost effectiveness estimates?	For Population 1 and Population 4, the EAG revision had no effect on cost effectiveness results, i.e., ribociclib+AI dominated abemaciclib+ET and dominated ET.
What additional evidence or analyses might help to resolve this key issue?	Ask the company to generate cost effectiveness results using relevant utility values from the MONALEESA-2 and MONALEESA-3 trial.

AI=aromatase inhibitor; DR=distant recurrence; EAG=External Assessment Group; ET=endocrine therapy; HRQoL=health-related quality of life; NMR=non-metastatic recurrence

1.6 Summary of EAG's preferred assumptions and resulting ICER

Table B Probabilistic pairwise results (ribociclib+AI versus ET, Population 1), PAS price for ribociclib and alpelisib

Scenario/EAG revisions	Incremental		ICER £/QALY	NMB (WTP=£30,000)
	Costs	QALYs		
A2. Company FAC base case	[redacted]	[redacted]	Dominant	£16,155
B1. EAG alternative base case	[redacted]	[redacted]	£15,030	£9,300

AI=aromatase inhibitor; EAG=External Assessment Group; ET=endocrine therapy; FAC=factual accuracy check; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; PAS=Patient Access Scheme; QALYs=quality adjusted life year; WTP=willingness to pay

Table C Probabilistic pairwise results (ribociclib+AI versus abemaciclib+ET, Population 4*), PAS price for ribociclib and alpelisib

Scenario/EAG revisions	Incremental		ICER £/QALY	NMB (WTP=£30,000)
	Costs	QALYs		
A2. Company FAC base case	[redacted]	[redacted]	Dominant	£43,349
B1. EAG alternative base case	[redacted]	[redacted]	Dominant	£43,485

* Model Population 4B
AI=aromatase inhibitor; EAG=External Assessment Group; ET=endocrine therapy; FAC=factual accuracy check; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; PAS=Patient Access Scheme; QALYs=quality adjusted life year; WTP=willingness to pay

Table D Probabilistic pairwise results (ribociclib+AI versus ET, Population 4*), PAS price for ribociclib and alpelisib

Scenario/EAG revisions	Incremental		ICER £/QALY	NMB (WTP=£30,000)
	Costs	QALYs		
A2. Company FAC base case	[redacted]	[redacted]	Dominant	£21,924
B1. EAG alternative base case	[redacted]	[redacted]	£10,548	£14,808

* Model Population 4B
AI=aromatase inhibitor; EAG=External Assessment Group; ET=endocrine therapy; FAC=factual accuracy check; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; PAS=Patient Access Scheme; QALYs=quality adjusted life year; WTP=willingness to pay

For further details of the exploratory and sensitivity analyses carried out by the EAG, see Section 6.1 to Section 6.7.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This appraisal focuses on ribociclib with an aromatase inhibitor (ribociclib+AI) as an adjuvant treatment option for patients with hormone receptor-positive (HR-positive), human epidermal growth factor receptor 2-negative (HER2-negative) early breast cancer.

In this External Assessment Group (EAG) report, references to the company submission (CS) are to the company's Document B, which is the company's full evidence submission. Additional evidence was provided by the company during the clarification stage.

2.2 Background

2.2.1 Early breast cancer

Breast cancer develops in the ducts or lobules of the breast and is a heterogeneous disease. Prognosis and treatment depend on many factors, including disease stage, hormone receptor status (oestrogen receptor-positive and/or progesterone receptor-positive), HER2 status and the presence of pathogenic variants such as the BReast CAncer (BRCA) gene. It is estimated that approximately 70% of patients with breast cancer have HR-positive, HER2-negative breast cancer.[1]

In the UK, approximately 56,400 women and 390 men are diagnosed with breast cancer each year and approximately 85% of female patients and 72% of male patients are diagnosed with early breast cancer (Stage I or Stage II).[2] In England, reported 5-year survival rates are nearly 100% for women diagnosed with Stage I breast cancer and approximately 90% for women diagnosed with Stage II breast cancer.[3] In a pooled analysis of randomised controlled trial (RCT) data,[4] 10-year distant recurrence risks (2000 to 2009) were:

- 7.3% for patients with node-negative HR-positive breast cancer
- 14.7% for patients with node-positive HR-positive breast cancer with one to three positive nodes
- 28.5% for patients with node-positive HR-positive breast cancer with four to nine positive nodes.

2.2.2 Ribociclib

Ribociclib is a cyclin-dependent kinase (CDK) 4/6 inhibitor. Ribociclib prevents the phosphorylation of retinoblastoma proteins to stop cell proliferation.[5]

Ribociclib is administered orally and is available as 200mg tablets.[6] The recommended dose for patients with HR-positive, HER2-negative early breast cancer is 400mg ribociclib once daily (QD) for the first 21 days of a 28-day treatment cycle for ≤36 months or until disease

recurrence or unacceptable toxicity occur.[6] It is recommended that, from commencement of treatment with ribociclib, an AI is taken QD continuously for 60 months.[6] For premenopausal women, perimenopausal women and men, ribociclib+AI should be used in combination with a luteinising hormone-releasing hormone (LHRH) agonist.[6]

If patients are unable to tolerate 400mg ribociclib QD, it is recommended that the dose is reduced to 200mg QD.[6] If a further dose reduction is required, ribociclib should be discontinued.[6] Dose interruptions until recovery are recommended for patients who experience Grade 2 or Grade 3 hepatobiliary toxicity, QT prolongation, Grade 2 pneumonitis and/or other Grade 3 toxicities.[6]

Ribociclib is not yet licensed in the UK as an adjuvant treatment option for patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence. European Medicines Agency (EMA) approval was received in November 2024[7] and Medicines and Healthcare products Regulatory Agency (MHRA) approval is expected in [redacted] (company response to factual accuracy check). The anticipated UK licensed indication is "[redacted]" (CS, Table 2).

2.3 Company's overview of current service provision

The company has presented the current National Health Service (NHS) treatment pathway for patients with HR-positive, HER2-negative early breast cancer and the positioning of ribociclib+AI, should ribociclib+AI be recommended by National Institute of Health and Care Excellence (NICE) for routine commissioning (CS, Figure 4). The treatment pathway was informed by the NICE early and locally advanced breast cancer diagnosis and management guidelines (NG101),[8] which were updated in January 2024.

The company has positioned ribociclib+AI as an alternative adjuvant treatment to endocrine therapy (ET) for patients with node-positive or node-negative, HR-positive, HER2-negative early breast cancer whose disease is at high risk of recurrence and as an alternative adjuvant treatment to abemaciclib+ET for patients with node-positive, HR-positive, HER2-negative early breast cancer whose disease is at high risk of recurrence, as defined in TA810[9]:

- ≥4 positive axillary lymph nodes, or
- 1 to 3 positive axillary lymph nodes, and at least one of the following criteria:
    - grade 3 disease (defined as ≥8 points on the modified Bloom–Richardson grading system or equivalent), or
    - primary tumour size ≥5 cm.

The company's positioning of ribociclib+AI is in line with its anticipated licensed indication.

Clinical advice to the EAG is that, for high risk patients, in NHS clinical practice, ET can include:

- non-steroidal AIs only (i.e., anastrozole and letrozole)
- steroidal AIs only (i.e., exemestane)
- AI in combination with ovarian suppression (for premenopausal women)
- tamoxifen in combination with ovarian suppression (for premenopausal women)
- tamoxifen only (for men).

Clinical advice to the EAG is that, with regard to adjuvant therapy, approximately 90% to 95% of NHS patients with HR-positive, HER2-negative early breast cancer whose disease is at high risk of recurrence receive anastrozole or letrozole, approximately 5% of NHS patients receive exemestane and few NHS patients receive tamoxifen.

In NG101,[8] it is recommended that tamoxifen is offered as "the initial adjuvant endocrine therapy for men and premenopausal women with ER [oestrogen receptor]-positive invasive breast cancer". However, clinical advice to the EAG is that most premenopausal women will receive an AI in combination with ovarian suppression because this combination is more effective than tamoxifen.

2.4 Critique of company's definition of decision problem

A summary of the final scope[10] issued by NICE and the decision problem addressed by the company is presented in Table 1. More information regarding key issues is provided in Section 2.4.1 to Section 2.4.7.

Table 1 Summary of the decision problem

	Final scope[10] issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment

Population	Adults with HR-positive, HER2-negative early breast cancer after surgery of the primary breast tumour.	Adults with HR-positive, HER2-negative early breast cancer **at high risk of recurrence** after surgery of the primary breast tumour.
		
		The population specified in the NICE final scope[10] is broader than the population addressed in the CS.
		
		The population addressed in the CS (Population 1 [NATALEE trial ITT population: patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence]) is in line with the anticipated UK marketing authorisation extension for ribociclib.
		
		The criteria used to define "high risk of recurrence" is aligned to the NATALEE trial eligibility criteria:
		• Anatomical Stage IIA
		  ○ N0, with
		  ▪ Grade 3, or
		  ▪ Grade 2, with any of the following criteria: Ki-67≥20%, Oncotype DX, Breast Recurrence Score≥26, Prosigna/PAM50 categorised as high risk, MammaPrint categorised as high risk, or EndoPredict EPclin Risk Score categorised as high risk
		  ○ N1
		• Anatomical Stage IIB:
		  ○ N0 or N1
		• Anatomic Stage III:
		  ○ N0, N1, N2 or N3
		
		In the CS, treatment after surgery of the primary breast tumour is referred to as adjuvant therapy
			Clinical advice to the EAG is that the company's definition of high risk of recurrence was reasonable.
			The company has provided clinical effectiveness results for several populations; see subgroup section for more information.

	Final scope[10] issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
Intervention	Ribociclib+AI	Ribociclib+AI	Ribociclib is not yet licensed in the UK as a treatment option for patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence. Medicines and Healthcare products Regulatory Agency approval is expected in [redacted].
Comparator(s)	**Full population** • Standard ET **For node-positive early breast cancer at high risk of recurrence** • Abemaciclib (+ET) **For high-risk early breast cancer with BRCA1 or 2 mutations** • Olaparib (with or without ET)	The relevant comparators for the following populations are: **Population 1 (NATALEE ITT) HR-positive, HER2-negative early breast cancer at high risk of recurrence:** • Standard ET (anastrozole, letrozole, exemestane and tamoxifen) **Population 2 (node-positive high-risk)** • ET **Population 3 (node-negative high-risk)**; • ET **Population 4 (node-positive high-risk eligible for abemaciclib; population evaluated in TA810[9])**: • Abemaciclib+ET • ET The company considers that olaparib is not a relevant comparator.	The EAG agrees that abemaciclib+ET and ET are relevant comparators. The EAG agrees with the company that olaparib is not a relevant comparator for this appraisal.
Outcomes	The outcome measures to be considered include: • OS • iDFS • DDFS • AEs • HRQoL	The outcome measures considered in this submission include: • OS • iDFS • DDFS • AEs • HRQoL	None

	Final scope[10] issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
Economic analysis	The cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective.	As per the NICE reference case.	None
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • node positive/negative disease • risk of recurrence • presence of germline BRCA1 or 2 mutations	The company considered the following three subpopulations (with the relevant comparators listed accordingly): • Population 2 (NATALEE trial node-positive high-risk): ET • Population 3 (NATALEE trial node-negative high-risk): ET • Population 4 (node-positive high-risk eligible for abemaciclib+ET as evaluated in TA810[9]): abemaciclib+ET and ET The company considered that abemaciclib+ET was not a relevant comparator for Population 2 or Population 3 because not all patients in Population 2 would be eligible for treatment with abemaciclib+ET and abemaciclib+ET is not recommended for patients with node-negative early breast cancer.	The EAG requested clinical and cost effectiveness data for patients ineligible for treatment with abemaciclib+ET (Population 5) (clarification questions A2 and B1). The EAG considers that Population 4 and Population 5 are most representative of patients seen in NHS clinical practice. Clinical advice to the EAG is that patients who are not eligible for abemaciclib+ET are treated with ET regardless of the nodal status of their breast cancer. This means that Population 2 and Population 3 are less relevant than Populations 1, 4 and 5.
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	The company considered that there will be no equality concerns related to this appraisal. The anticipated future licensed indication will include men and women, as included in the NATALEE trial	None

AEs=adverse events; AI=aromatase inhibitor; BRCA=BReast CAncer gene; CS=company submission; DDFS=distant disease-free survival; DX=diagnosis; EAG=External Assessment Group; EPclin=EndoPredict; ESMO=European Society for Medical Oncology; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; HRQoL=health-related quality of life; iDFS=invasive disease-free survival; ITT=intention-to-treat; Ki-67=Kiel 67; NHS=National Health Service; NICE=National Institute for Health and Care Excellence; OS=overall survival; PAM50=Prediction Analysis of Microarray 50; PSS=Personal Social Services
Source: CS, Table 1

2.4.1 Evidence sources

The primary source of direct clinical effectiveness evidence presented by the company for the comparison of ribociclib+AI versus AI was the NATALEE trial[11] (Table 2).

In the absence of direct clinical effectiveness evidence for the comparison of ribociclib+AI versus abemaciclib+ET, the company used aggregate data from the monarchE trial[12] (Table 2) to inform indirect treatment comparisons (ITCs).`

Table 2 Key characteristics of the NATALEE and monarchE trials

Trial	Study design	Intervention	Comparator	Population
NATALEE trial	Ongoing, phase III, multi-centre, international, open-label RCT	Ribociclib+AI (anastrozole or letrozole) (n=2549)	AI (anastrozole or letrozole) (n=2552)	Patients with node-negative or node-positive, HR-positive, HER2-negative early breast cancer at high risk of recurrence
monarchE trial[12]	Ongoing, phase III, multi-centre, international, open-label RCT	Abemaciclib+ET (anastrozole, letrozole, exemestane or tamoxifen) (n=2555)	ET (anastrozole, letrozole, exemestane or tamoxifen) (n=2565)	Patients with node-positive, HR-positive, HER2-negative early breast cancer at high risk of recurrence with pathological tumour involvement in: • ≥4 ipsilateral ALNs, or • 1 to 3 ALNS with either grade 3 disease or primary tumour size ≥5 cm

AI=aromatase inhibitor; ALN=axillary lymph node; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; RCT=randomised controlled trial

2.4.2 Population

The NATALEE trial intention-to-treat (ITT) population is in line with the anticipated UK licensed indication for ribociclib (see Section 2.2.2 and CS, Table 2). The NATALEE trial includes patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence after primary breast tumour surgery. The company defined high risk of recurrence as per the NATALEE trial eligibility criteria (CS, Section 1.1). Clinical advice to the EAG is that the company's definition of high risk of recurrence is reasonable. The company only considered patients at high risk of recurrence; a population that is narrower than the population described in the final scope[10] issued by NICE.

The company has provided NATALEE trial clinical effectiveness evidence relating to four populations (Population 1, Population 2, Population 3 and Population 4). In the company clarification response, the company updated the definition of Population 4, using the terms Population 4a and Population 4b. In addition, in response to clarification question A2, the company provided baseline characteristics and clinical effectiveness results for two further populations (Population 5 and Population 6). Definitions of all seven populations are provided in Table 3.

Table 3 Populations

Population	Company definition	EAG comment	NATALEE trial ITT population n (%)
NATALEE trial ITT population			
Population 1	Patients with node-negative or node-positive, HR-positive, HER2-negative early breast cancer at high risk of recurrence.	Includes patients eligible and ineligible for abemaciclib+ET. The only relevant comparator for this population is ET.	5101 (100)
NATALEE trial subpopulations			
Population 2 (pre-specified)	Patients with node-positive, HR-positive, HER2-negative early breast cancer at high risk of recurrence.	Includes patients eligible and ineligible for abemaciclib+ET. The only relevant comparator for this population is ET.	4480 (87.8)
Population 3 (pre-specified)	Patients with node-negative, HR-positive, HER2-negative early breast cancer at high risk of recurrence.	Only includes patients ineligible for abemaciclib+ET. The only relevant comparator for this population is ET.	613 (12.0)
Population 4a (NATALEE trial selected, unweighted population; data used in the direct clinical effectiveness comparison)	Patients with node-positive, HR-positive, HER2-negative early breast cancer at high risk of recurrence who are eligible for treatment with abemaciclib+ET (population evaluated in TA810[9]).	Includes patients eligible for abemaciclib+ET. In response to clarification question A1 and A2, the company confirmed that Population 4, Population 4a, the 'NATALEE-selected population' and the 'NATALEE-selected unweighted population' refer to the same population. The relevant comparators for this population are abemaciclib+ET and ET.	[redacted]
Population 4b (NATALEE trial selected, reweighted population; data used in the indirect clinical effectiveness comparison)	NATALEE trial-selected patients with baseline patient characteristics reweighted to match the monarchE Cohort 1 patient characteristics.		ESS: [redacted]
EAG requested populations			
Population 5	Patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence who are not eligible for treatment with abemaciclib+ET.	Clinical advice to the EAG is that patients who are not eligible for abemaciclib+ET are treated with ET regardless of the nodal status of their breast cancer. The only relevant comparator is ET.	[redacted]
Population 6	Patients with node-positive, HR-positive, HER2-negative early breast cancer at high risk of recurrence who are not eligible for treatment with abemaciclib+ET.	The only relevant comparator is ET.	[redacted]

CS=company submission; EAG=External Assessment Group; ESS=estimated sample size; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; ITT=intention-to-treat
Source: CS, Section 1.1 and Table 10; company response to clarification question A1 and A2

2.4.3 Intervention

The company has presented evidence for ribociclib as per its anticipated UK licensed indication (CS, Table 2). Further details are provided in Section 2.2.2.

2.4.4 Comparators

Abemaciclib+ET

Over half of NATALEE trial Population 1 ([redacted]/5101 patients, [redacted]) would, if treated in the NHS, be eligible for treatment with abemaciclib+ET, as per the NICE TA810[9] recommendation.

The company carried out matching-adjusted indirect comparisons (MAICs) using individual patient-level data (IPD) from the NATALEE trial and aggregate data from the monarchE trial[12] to provide indirect clinical effectiveness evidence for the comparisons of ribociclib+AI versus abemaciclib+ET for Population 4 (population evaluated in TA810[9]). In the monarchE trial,[12] available ET therapies were anastrozole, letrozole, exemestane, tamoxifen and toremifene, with or without ovarian suppression; 69% of monarchE trial patients received an AI and 31% received tamoxifen.[13]

The EAG asked the company (clarification question A9) to carry out simulated treatment comparisons (STCs) for the comparison of ribociclib+AI versus abemaciclib+ET.

Endocrine therapy

In the NHS, patients who are not eligible for treatment with abemaciclib+ET are treated with ET.

Clinical advice to the EAG is that, in NHS clinical practice, patients may receive anastrozole, letrozole, exemestane and tamoxifen (as standard ET); however, most NHS patients with HR-positive, HER2-negative early breast cancer receive either anastrozole or letrozole, i.e., an AI (see Section 2.3).

The company has presented direct clinical effectiveness evidence from the NATALEE trial for the comparison of ribociclib+AI versus AI (Population 1); in the NATALEE trial, the permitted AIs were anastrozole and letrozole (investigators' choice).

The company has presented iDFS and OS results for the comparison of ribociclib+AI versus ET (Table 33 and Table 34); in both sets of analyses, the company has used NATALEE trial AI data to generate results versus ET:

- Population 4/4a: before matching, unweighted analysis, i.e. direct NATALEE trial results (patients eligible for abemaciclib+ET)
- Population 4/4b: matched, reweighted IPD analysis (patients eligible for abemaciclib+ET)

The EAG considers that the company before matching, unweighted analysis results should be used to inform decision-making for the comparison of ribociclib+AI versus ET.

Excluded comparator (olaparib)

The company considered (and the EAG agrees) that olaparib is not a relevant comparator for this appraisal. Olaparib is recommended by NICE[14] as an adjuvant treatment option for patients with HER2-negative, BRCA1/2-positive, high-risk early breast cancer that has been treated with neoadjuvant or adjuvant chemotherapy. Clinical advice to the company (CS, Appendix Q.2 and Appendix Q.3) and to the EAG is that only a small proportion of NHS patients with early breast cancer have BRCA1/2-positive disease and that for patients with BRCA1/2-positive, HR-positive, HER2-negative early breast cancer, targeted therapy would be prioritised and therefore these patients would be treated with olaparib before being treated with ribociclib.

2.4.5 Outcomes

Clinical advice to the EAG is that the outcomes listed in the final scope[10] issued by NICE are the most relevant outcomes for patients with early breast cancer. The NATALEE trial primary endpoint is invasive disease-free survival (iDFS), assessed by the investigator using the Standardised Definitions for Efficacy End Points (STEEP) criteria.[15] Secondary endpoints include recurrence-free survival (RFS), distant disease-free survival (DDFS), overall survival (OS), health-related quality of life (HRQoL), adverse events (AEs) and pharmacokinetics. Definitions of NATALEE trial outcome measures are provided in the CS (CS, Table 6).

To generate iDFS, DDFS, OS and treatment-emergent AEs (TEAEs) results, the company carried out unanchored MAICs (CS, Section 2.8.5) and STCs (company response to clarification question A9) for the comparison of ribociclib+AI versus abemaciclib+ET; for the comparison of ribociclib+AI versus ET, the company carried out reweighted IPD analyses (also referred to by the company as a MAIC).

The company stated that “iDFS is considered a clinically meaningful surrogate endpoint for OS, as disease recurrence is associated with breast cancer mortality” (CS, p65) and that “observed improvements in these endpoints [iDFS and DDFS] are anticipated, in the long-term, to translate into improvements in OS” (CS, p37). Clinical advice to the EAG is that DDFS is a more appropriate proxy for OS than iDFS.

2.4.6 Economic analysis

As specified in the final scope[10] issued by NICE, the cost effectiveness of treatments was expressed in terms of incremental cost effectiveness ratios (ICERs) per quality adjusted life year (QALY) gained. Outcomes were assessed over a 50-year time horizon (which the

company considered was equivalent to a lifetime horizon) and costs were considered from an NHS perspective.

Ribociclib, abemaciclib, alpelisib and palbociclib are available to the NHS at confidential Patient Access Scheme (PAS) prices. Only the confidential prices of ribociclib and alpelisib are known to the company. Cost effectiveness results generated using the discounted prices for all drugs are presented in a confidential appendix.

The EAG agrees with the company that a severity weighting was not applicable for this appraisal (see CS, Section B.3.6 for details).

Cost effectiveness results for patients ineligible for treatment with abemaciclib+ET

Company iDFS results are available for Population 1, Population 4 and Population 5 (Table 4). In response to clarification question B1, the company claimed that the efficacy of ribociclib+AI versus AI was the same irrespective of whether patients were eligible or ineligible for treatment with abemaciclib+ET; the data to support this claim are presented in Table 4.

As the company has not presented Population 5 cost effectiveness results, the EAG has used Population 1 cost effectiveness results as a proxy for Population 5 cost effectiveness results. The EAG highlights that Population 5 ICERs per QALY gained may be overestimated/conservative as NATALEE trial Population 5 iDFS results are slightly more favourable than Population 1 results.

Table 4 NATALEE trial iDFS results

	Population 1 (ITT population)	Population 4 (patients eligible for abemaciclib+ET)	Population 5 (patients not eligible for abemaciclib+ET)
	Ribociclib+AI vs AI		
HR (95% CI)	0.715 (0.609 to 0.840)	[redacted][a]	[redacted]

[a] Data extracted from company response to clarification question A2, Table 1; iDFS for the comparison of ribociclib+AI vs AI was reported as HR [redacted] (95% CIs [redacted] to [redacted]), p=[redacted] in CS, Table 33
AI=aromatase inhibitor; CI=confidence interval; CS=company submission; HR=hazard ratio; iDFS=invasive disease-free survival
Source: CS, Table 16 and company response to clarification question A2, Table 5

2.4.7 Subgroups

Three subgroups are listed in the final scope[10] issued by NICE, namely nodal positive/negative disease, risk of recurrence and presence of germline GRCA1 or 2 mutations.

Nodal status

The company presented (CS, Section 2.6.5) iDFS subgroup analysis results for patients with node-positive disease (Population 2) and patients with node-negative disease (Population 3).

Risk of recurrence

The company did not present results stratified by risk of recurrence because the NATALEE trial ITT population only included patients with high risk of recurrence.

Presence of germline BRCA1 or 2 mutations

The company did not present results stratified by presence of BRCA1/2 mutations because the company considered (and the EAG agrees) that ribociclib+AI would not displace olaparib for patients with BRCA1/2-positive early breast cancer (see Section 2.4.4).

Clinical advice to the EAG is that it was reasonable for the company not to present subgroup results stratified by the presence of BRCA1/2 mutations because only a small proportion (5% to 7%) of NHS patients with early breast cancer have BRCA1/2-positive disease. Furthermore, clinical advice to the EAG is that not all patients with BRCA1/2-positive, HR-positive, HER2-negative early breast cancer are likely to be identified in NHS clinical practice because BRCA1/2 genetic testing is only offered to:

- female patients aged <50 years with triple-negative breast cancer (NG101)[8] or bilateral breast cancer
- female patients with no personal history of breast cancer but who have an available affected relative if that relative has a combined BRCA1 and BRCA2 mutation carrier probability of ≥10% (NICE familial breast cancer clinical guidelines [CG164][16])
- female patients with high grade non-mucinous ovarian cancer
- male patients.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company conducted a systematic literature review (SLR) to identify and select clinical effectiveness evidence for ribociclib+ET and other relevant treatments (including abemaciclib+ET and ET) for patients with HR-positive, HER2-negative early breast cancer. Full details of the company's methods are presented in the CS (CS, Appendix D). The company's literature searches were comprehensive and were updated <6 months before the company's evidence submission to NICE. An assessment of the extent to which the company's SLR was conducted in accordance with the EAG's in-house systematic review checklist is summarised in Table 5. The EAG considers that the company's systematic review methods were appropriate.

Table 5 EAG appraisal of the company's systematic review methods

Review process	EAG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	See CS, Appendix D.1.3, Table 6
Were appropriate sources searched?	Yes	See CS, Appendix D.2
Was the timespan of the searches appropriate?	Yes	See CS, Appendix D.1.3, Table 6 Sources were searched from database inception
Were appropriate search terms used?	Yes	See CS, Appendix D.2, Table 1 to Table 3
Were the eligibility criteria appropriate to the decision problem?	Yes	See CS, Appendix D.1.3, Table 6 The SLR eligibility criteria included studies of "ribociclib plus AI and other relevant treatment options" (CS, Appendix D.1) and thus the company SLR eligibility criteria led to the inclusion of more treatments than listed in the final scope[10] issued by NICE
Was study selection applied by two or more reviewers independently?	Yes	See CS, Appendix D.3
Were data extracted by two or more reviewers independently?	Yes	See CS, Appendix D.3 One reviewer extracted data, and these data were checked by a second (independent) reviewer
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	See CS, Section 2.4.2, Table 14 and CS, Appendix D.10, Table 23 The company assessed the quality of the NATALEE and monarchE[12] trials using the quality assessment checklist for clinical trials[17] devised by the CRD at the University of York
Was the quality assessment conducted by two or more reviewers independently?	Yes	See company response to clarification question C7 One reviewer quality assessed the included trials and quality assessments were checked by a second (independent) reviewer
Were attempts to synthesise evidence appropriate?	Yes	The company performed MAICs (CS, Section 2.8) and STCs (company response to clarification question A8) to provide clinical effectiveness evidence for the comparison of ribociclib+AI versus abemaciclib+ET. See Section 3.4 for the company's methods and the EAG's critique of the ITCs

AI=aromatase inhibitor; CRD=Centre for Reviews and Dissemination; CS=company submission; EAG=External Assessment Group; ET=endocrine therapy; ITC=indirect treatment comparison; MAIC=matching-adjusted indirect comparison; SLR=systematic literature review; STC=simulated treatment comparison
Source: EAG in-house checklist

3.2 Critique of main trial of the technology of interest, the company's analysis and interpretation

3.2.1 Included trials

The company SLR eligibility criteria led to the inclusion in the review of more treatments than were listed in the final scope[10] issued by NICE. In addition to studies of ribociclib+ET, abemaciclib+ET and ET, the company searched for studies of treatments that are not routinely used in NHS clinical practice (CS, Appendix D.3, Table 6)

The company identified two trials, namely the NATALEE trial (ribociclib+AI versus AI; Section 3.2.2 to Section 3.2.5) and the monarchE trial[12] (abemaciclib+ET versus ET; CS, Section 3.4.1 to Section 3.4.2).

3.2.2 Characteristics of the NATALEE trial

The key characteristics of the NATALEE trial are presented in Table 6.

Table 6 Key characteristics of the NATALEE trial

Trial parameter	NATALEE trial (N=5101)
Design	• Ongoing, phase III, multi-centre, international, open-label, randomised controlled trial • 387 centres across 20 countries: Argentina, Australia, Austria, Belgium, Brazil, Canada, China, France, Germany, Hungary, Ireland, Italy, Republic of Korea, Poland, Romania, Russian Federation, Spain, Taiwan, UK (83 patients from 11 UK centres) and US
Population	• Patients (≥18 years) with histologically confirmed unilateral primary invasive adenocarcinoma of the breast ≤18 months prior to randomisation, or multicentric and/or multifocal tumour if all histopathologically examined lesions meet pathologic inclusion criteria • Breast cancer (and all multicentric and/or multifocal tumour lesions) must be confirmed ER-positive and/or PR-positive and HER2-negative • Breast cancer must be Anatomic Stage Group II that is N1 or N0 with Grade 2 or 3 and/or Ki67≥20% or Anatomic Stage Group III • Post-surgical resection where tumour was removed completely • ECOG PS 0 to 1 • For female patients, menopausal status must be known
Intervention	• 400mg QD oral ribociclib for the first 21 days of a 28-day treatment cycle for ≤36 months plus • 2.5mg QD letrozole or 1mg QD anastrozole[a] continuously (plus 3.6mg goserelin once every 28-day treatment cycle for premenopausal women and men) for 60 months
Comparator	• 2.5mg QD letrozole or 1mg QD anastrozole[a] continuously (plus 3.6mg goserelin once every 28-day treatment cycle for premenopausal women and men) for 60 months
Primary outcome	• iDFS
Secondary outcomes	• RFS, DDFS, OS, PROs (EORTC QLQ-C30, EORTC QLQ-BR23, EQ-5D-5L and HADS), safety and pharmacokinetics
Data cut-offs presented in CS	• Latest DCO: 29th April 2024[11] • iDFS PA DCO: 21st July 2023[18] • IA3 DCO: 11th January 2023[19]

[a] Investigator's choice
CS=company submission; DCO=data cut-off; DDFS=distant disease-free survival; ECOG PS=Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-BR23=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire breast cancer module; EQ-5D-5L=EuroQol-5 Dimensions-5 Levels; ER=oestrogen receptor; HADS=Hospital Anxiety and Depression Scale; HER2=human epidermal growth factor receptor 2; IA3=interim analysis 3; iDFS=invasive disease-free survival; Ki-67= antigen Kiel-67; OS=overall survival; PA=primary pre-planned analysis; PR=progesterone receptor; PROs=patient-reported outcomes; QD=once daily; RFS=recurrence-free survival
Source: CS, Table 5 to Table 8

Clinical advice to the EAG is that it was reasonable that letrozole and anastrozole were the only permitted ETs in the NATALEE trial; in the NHS, most patients receive either letrozole or anastrozole. However, clinical advice to the company (CS, Appendix Q.3, Table 110) is that [redacted] of patients receive letrozole, [redacted] receive anastrozole and the remainder are likely to receive exemestane ([redacted]) or tamoxifen ([redacted]).

3.2.3 Characteristics of the NATALEE trial patients

The NATALEE trial Population 1 baseline characteristics, disease characteristics and prior therapy details are provided in the CS (Table 9, Table 10 and Table 11, respectively).

Clinical advice to the EAG is that, overall, Population 1 baseline characteristics are representative of NHS patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence, with the exception that fewer NATALEE trial patients are post-menopausal (2848/5101, 55.8%) and fewer patients have node-negative disease (1431/5101, 28.1% at diagnosis) than is expected in NHS clinical practice.

In response to clarification question A2, the company provided NATALEE trial baseline characteristics for Population 4, Population 5 and Population 6. In response to clarification question A3, the company also provided baseline characteristics for Population 2 and Population 3.

The baseline characteristics of Population 1, Population 4 and Population 5 are provided in Table 7.

Table 7 Baseline characteristics of Population 1, Population 4 and Population 5

	Population 1 (ITT)		Population 4 (abemaciclib+ET eligible)		Population 5 (abemaciclib+ET ineligible)	
Characteristic	**Ribociclib+AI (n=2549)**	**AI (n=2552)**	**Ribociclib+AI (n=[redacted])**	**AI (n=[redacted])**	**Ribociclib+AI (n=[redacted])**	**AI (n=[redacted])**
Female, n (%)	2538 (99.6)	2543 (99.6)	[redacted]	[redacted]	[redacted]	[redacted]
Age, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race						
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS						
0	2106 (82.6)	2132 (83.5)	[redacted]	[redacted]	[redacted]	[redacted]
1	440 (17.3)	418 (16.4)	[redacted]	[redacted]	[redacted]	[redacted]
Missing	3 (0.1)	2 (0.1)	[redacted]	[redacted]	[redacted]	[redacted]
Histopathological grade at diagnosis						
GX	30 (1.2)	32 (1.3)	[redacted]	[redacted]	[redacted]	[redacted]
G1	218 (8.6)	240 (9.4)	[redacted]	[redacted]	[redacted]	[redacted]
G2	1458 (57.2)	1451 (56.9)	[redacted]	[redacted]	[redacted]	[redacted]
G3	521 (20.4)	549 (21.5)	[redacted]	[redacted]	[redacted]	[redacted]
Not done	292 (11.5)	258 (10.1)	[redacted]	[redacted]	[redacted]	[redacted]
Missing	30 (1.2)	22 (0.9)	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	Population 1 (ITT)		Population 4 (abemaciclib+ET eligible)		Population 5 (abemaciclib+ET ineligible)	
	Ribociclib+AI (n=2549)	AI (n=2552)	Ribociclib+AI (n=[redacted])	AI (n=[redacted])	Ribociclib+AI (n=[redacted])	AI (n=[redacted])
T stage at diagnosis						
TX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
N stage at diagnosis						
NX	272 (10.7)	264 (10.3)	[redacted]	[redacted]	[redacted]	[redacted]
N0	694 (27.2)	737 (28.9)	[redacted]	[redacted]	[redacted]	[redacted]
N1	1050 (41.2)	1049 (41.1)	[redacted]	[redacted]	[redacted]	[redacted]
N2	332 (13.0)	292 (11.4)	[redacted]	[redacted]	[redacted]	[redacted]
N3	151 (5.9)	175 (6.9)	[redacted]	[redacted]	[redacted]	[redacted]
Missing	50 (2.0)	35 (1.4)	[redacted]	[redacted]	[redacted]	[redacted]
Time since initial diagnosis (months), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AJCC stage						
Stage I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AI=aromatase inhibitor; AJCC=American Joint Committee on Cancer; CS=company submission; ECOG PS: Eastern Cooperative Oncology Group performance status; ET=endocrine therapy; ITT=intention-to-treat; M=metastases; N=node; SD=standard deviation; T=tumour
Source: CS, Table 9 and Table 10; company response to clarification question A2

Baseline characteristics were balanced across the populations with the exceptions that compared to Population 1 and Population 5, Population 4 included a higher proportion of patients who had:

- T3 and T4 stage disease at diagnosis
- N2 and N3 stage disease at diagnosis
- American Joint Committee on Cancer (AJCC) Stage III disease.

The company did not provide menopausal status data for Population 4 and Population 5.

3.2.4 Quality assessment of the NATALEE trial

The company assessed (CS, Table 14) the quality of the NATALEE trial using the quality assessment checklist for RCTs[17] devised by the Centre for Reviews and Dissemination (CRD) at the University of York. The company's assessments and EAG comments are presented in Table 8. The EAG's assessment is that the NATALEE trial is of good methodological quality.

Table 8 Quality assessment of the NATALEE trial

Quality assessment item	Company	EAG	EAG comment
Was the randomisation carried out appropriately?	Low	Low	Randomisation was stratified and completed using IRT (CS, Table 6)
Was the concealment of treatment allocation adequate?	Unclear	Low	Randomisation was stratified and completed using IRT (CS, Table 6)
Were the groups similar at the outset of the study in terms of prognostic factors?	Low	Low	Clinical advice to the EAG is that the NATALEE trial patient baseline characteristics (CS, Table 9 to Table 11) were well-balanced across the treatment arms
Were the care providers, participants and outcome assessors blind to treatment allocation?	High	Unclear	The NATALEE trial was an open-label trial and outcomes were investigator-assessed. However, the secondary endpoint, OS, is an objective measure and therefore is not subject to bias. The primary endpoint (iDFS), the secondary endpoints (RFS, DDFS) and safety, may have been subject to investigator and/or evaluation bias
Were there any unexpected imbalances in drop-outs between groups?	Low	Low	A slightly lower proportion of patients in the ribociclib+AI arm ([redacted], [redacted]) discontinued treatment than in the AI arm ([redacted], [redacted]) (see NATALEE trial CSR [29 April 2024 DCO],[11] Table 1-2)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low	Low	-
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Low	Low	-

AI=aromatase inhibitor; CS=company submission; CSR=Clinical Study Report; DCO=data cut-off; DDFS=distant disease-free survival; EAG=External Assessment Group; iDFS=invasive disease-free survival; IRT=interactive response technology; OS=overall survival; RFS=recurrence-free survival
Source: CS, Table 14; NATALEE trial CSR (29 April 2024 DCO)[11]

3.2.5 Statistical approach adopted for the analysis of the NATALEE trial data

The company provided the NATALEE trial Clinical Study Report (CSR)[11] for the 29 April 2024 data cut-off (DCO),[11] the trial statistical analysis plan (TSAP)[20] and the trial protocol version 4.0.[21] The company presented a summary of the statistical analysis methods adopted for the analysis of NATALEE trial data (CS, Table 13). A summary of the EAG checks of the pre-planned statistical approach used by the company to analyse NATALEE trial data is provided in Table 9.

Table 9 EAG assessment of statistical approaches used in the NATALEE trial

Item	EAG assessment	Statistical approach with EAG comments
Were all analysis populations clearly defined and pre-specified?	Partial	The NATALEE trial analysis populations were clearly defined in CS, Table 12. Subgroup analysis populations were defined in the TSAP[20] (Section 2.2.6) The EAG notes that subgroup analysis stratified by patient eligibility for treatment with abemaciclib+ET was not a pre-specified subgroup analysis
Was an appropriate sample size calculation pre-specified?	Yes	See CS, Table 13
Were all protocol amendments made prior to analysis?	Yes	A summary of the NATALEE trial protocol amendments made between protocol v1.0 (27 August 2018) and protocol v4.0 (27 August 2020) was provided in protocol v4.0.[21] The EAG considers that all protocol amendments were appropriate and notes that all were made prior to the first DCO date (IA1 DCO: 3 September 2021)[19]
Were all primary and secondary efficacy outcomes pre-defined and analysed appropriately?	Yes	See NATALEE trial protocol v4.0,[21] Section 8.4 and 8.5 for outcome definitions. See NATALEE trial TSAP,[20] Section 2.5 to Section 2.7 for outcome definitions and planned analysis methods
Was the analysis approach for PROs appropriate and pre-specified?	Yes	See NATALEE trial protocol v4.0,[21] Section 8.5.2 and NATALEE trial TSAP,[20] Section 2.11
Was the analysis approach for AEs appropriate and pre-specified?	Yes	See NATALEE trial protocol v4.0,[21] Section 8.5.3 and NATALEE trial TSAP,[20] Section 2.8
Was a suitable approach employed for handling missing data?	Yes	See NATALEE trial TSAP,[20] Section 2.5.3, Section 2.7.3 and Section 2.11 for the methods for handling missing data for the primary outcome, the secondary outcomes and the PROs, respectively
Were all subgroup and sensitivity analyses pre-specified?	Partial	See NATALEE trial TSAP,[20] Section 2.2.6 for pre-specified subgroup analyses and Section 2.5.4 for pre-specified sensitivity analyses The EAG notes that subgroup analysis stratified by patient eligibility for treatment with abemaciclib+ET was not a pre-specified subgroup analysis

AE=adverse event; CS=company submission; DCO=data cut-off; EAG=External Assessment Group; IA1=interim analysis 1; PRO=patient-reported outcome; TSAP=trial statistical analysis plan
Source: CS, Table 12 and Table 13; NATALEE trial protocol version 4.0;[21] NATALEE trial TSAP;[20] NATALEE trial CSR (11 January 2023 DCO)[19]

3.3 NATALEE trial: efficacy results

NATALEE trial results for Population 1 from the most recent DCO (29 April 2024 DCO;[11] median follow-up: [redacted] months; median iDFS follow-up: 44.2 months) are summarised in Section 3.3.1.

3.3.1 Key efficacy results

iDFS (NATALEE trial primary outcome), RFS, DDFS and OS (NATALEE trial secondary outcomes) results from the 29 April 2024 DCO[11] for Population 1 are presented in Table 10. These data show that the NATALEE trial iDFS, RFS and DDFS hazard ratios (HRs) statistically significantly favoured ribociclib+AI over AI; however, for all three of these outcomes, the differences in 3-year and 4-year event rates between the NATALEE trial treatment arms were modest. The NATALEE trial OS HR numerically favoured ribociclib+AI over AI; however, differences in 3-year and 4-year OS event rates were modest.

Table 10 NATALEE trial key efficacy results: Population 1

	Ribociclib+AI (n=2549)	**AI (n=2552)**
iDFS		
Number of events, n (%)	263 (10.3)	340 (13.3)
HR (95% CI); p-value	0.715 (0.609 to 0.840); p<0.0001	
3-year iDFS rate, % (95% CI)	90.8 [redacted]	88.1 [redacted]
4-year iDFS rate, % (95% CI)	88.5 [redacted]	83.6 [redacted]
RFS		
Number of events, n (%)	[redacted]	[redacted]
HR (95% CI); p-value	[redacted]	
3-year RFS rate, % (95% CI)	[redacted]	[redacted]
4-year RFS rate, % (95% CI)	[redacted]	[redacted]
DDFS		
Number of events, n (%)	240 (9.4)	311 (12.2)
HR (95% CI); p-value	0.715 (0.604 to 0.847); p<0.0001	
3-year DDFS rate, % (95% CI)	91.6 [redacted]	89.2 [redacted]
4-year DDFS rate, % (95% CI)	89.4 [redacted]	84.9 [redacted]
OS		
Number of events, n (%)	105 (4.1)	121 (4.7)
HR (95% CI); p-value	0.827 (0.636 to 1.074); p=0.0766	
3-year OS rate, % (95% CI)	96.8 [redacted]	96.0 [redacted]
4-year OS rate, % (95% CI)	95.0 [redacted]	94.2 [redacted]

AI=aromatase inhibitor; CI=confidence interval; CS=company submission; DDFS=distant disease-free survival; HR=hazard ratio; iDFS=invasive disease-free survival; OS=overall survival; RFS=recurrence-free survival
Source: CS, Table 16, Table 18, Table 20 and Table 22

The company also provided key efficacy results from the primary pre-planned analysis (PA) 21 July 2023 DCO[18] (CS, Table 15, Table 17, Table 19 and Table 21) and the interim analysis 3 (IA3) 11 January 2023 DCO[19] (CS, Appendix N). Efficacy results from the earlier DCOs were consistent with the efficacy results from the most recent DCO (29 April 2024).[11]

3.3.2 Subgroup analyses

The company provided iDFS results for Population 2 (CS, Figure 19 and Figure 21) and Population 3 (CS, Figure 20 and Figure 22) from the most recent DCO (29 April 2024)[11] and from the PA 21 July 2023 DCO,[18] respectively.

NATALEE trial iDFS subgroup analysis results from the most recent DCO (29 April 2024)[11] for Population 2 and Population 3 are presented in Table 11, as per the final scope[10] issued by NICE (i.e., subgroup analysis stratified by node positive/negative disease; see Table 1).

Table 11 iDFS subgroup analyses results stratified nodal status

	Population 2 (node-positive, high-risk)		Population 3 (node-negative, high-risk)	
	Ribociclib+AI (n=2261)	AI (n=2219)	Ribociclib+AI (n=285)	AI (n=328)
Median follow-up, months	44.2		49.1	
Number of events, n (%)	240 (10.6)	301 (13.6)	23 (8.1)	38 (11.6)
HR (95% CI); p-value	0.731 (0.617 to 0.866); NR		0.666 (0.397 to 1.118); NR	
4-year rate, % (95% CI)	88.0 (NR)	83.0 (NR)	92.1 (NR)	87.0 (NR)

AI=aromatase inhibitor; CI=confidence interval; CS=company submission; HR=hazard ratio; iDFS=invasive disease-free survival; NR=not reported
Source: CS, Figure 18, Figure 21 and Figure 22

In response to clarification question A2, the company provided NATALEE trial results for the following populations:

- Population 4 (node-positive, high-risk, abemaciclib+ET ***eligible*** population)
- Population 5 (***only*** high-risk, abemaciclib+ET ***ineligible*** population)

NATALEE trial iDFS, RFS, DDFS and OS results for these two populations and Population 1 (29 April 2024 DCO)[11] populations are presented in Table 12.

Table 12 NATALEE trial iDFS, RFS, DDFS and OS results for Population 1, Population 4 and Population 5

	Population 1		Population 4 (abemaciclib+ET eligible)		Population 5 (abemaciclib+ET ineligible)	
	Ribociclib+AI (n=2549)	AI (n=2552)	Ribociclib+AI (n=[redacted])	AI (n=[redacted])	Ribociclib+AI (n=[redacted])	AI (n=[redacted])
iDFS						
Number of events, n (%)	263 (10.3)	340 (13.3)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI); p-value	0.715 (0.609 to 0.840); p<0.0001		[redacted][a]		[redacted]	
RFS						
Number of events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI); p-value	[redacted]		[redacted]		[redacted]	
DDFS						
Number of events, n (%)	240 (9.4)	311 (12.2)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI); p-value	0.715 (0.604 to 0.847); p<0.0001		[redacted]		[redacted]	
OS						
Number of events, n (%)	105 (4.1)	121 (4.7)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI); p-value	0.827 (0.636 to 1.074); p=0.0766		[redacted]		[redacted]	

[a] Data extracted from company response to clarification question A2, Table 1; iDFS for the comparison of ribociclib+AI vs AI was reported as HR [redacted] (95% CIs [redacted] to [redacted]), p=[redacted] in CS, Table 33
[b] Data extracted from company response to clarification question A2, Table 4; OS for the comparison of ribociclib+AI vs AI was reported as HR [redacted] (95% CIs [redacted] to [redacted]), p=[redacted] in CS, Table 34
AI=aromatase inhibitor; CI=confidence interval; CS=company submission; DDFS=distant disease-free survival; HR=hazard ratio; iDFS=invasive disease-free survival; OS=overall survival; RFS=recurrence-free survival
Source: CS, Table 16, Table 18, Table 20 and Table 22; company response to clarification question A2, Table 1 to Table 8

Compared to Population 1 and Population 5, Population 4 had [redacted] iDFS, RFS, DDFS and OS event rates. Population 1, Population 4 and Population 5 iDFS, RFS and DDFS HRs [redacted] ribociclib+AI over AI. Further, for all populations, OS HRs indicated [redacted] between ribociclib+AI and AI.

3.4 EAG summary and critique of the indirect comparisons

Direct clinical effectiveness evidence for the comparison of ribociclib+AI versus AI is available from the NATALEE trial. The company considered (and the EAG agrees) that ET and abemaciclib+ET are also relevant comparators to ribociclib+AI for patients with HR-positive, HER2-negative early breast cancer whose disease is at high risk of recurrence. The company carried out MAIC analyses to compare the clinical effectiveness of ribociclib+AI versus abemaciclib+ET for Population 4; abemaciclib+ET is only an appropriate treatment for Population 4 (i.e., patients with node-positive HR-positive, HER2-negative early breast cancer whose disease is at high risk of recurrence with pathological tumour involvement, as evaluated in TA810[9]).

In addition, for Population 4, the company carried out reweighted IPD analyses to compare the clinical effectiveness of ribociclib+AI versus ET. The EAG considers that the reweighted IPD analysis is not strictly an indirect comparison as it only utilises outcome data from the NATALEE trial; despite matching to monarchE trial[12] summary patient characteristics, it is an analysis of weighted NATALEE trial Population 4 IPD data (ribociclib+AI versus AI).

3.4.1 Studies included in the indirect comparisons

The company SLR identified two trials that provided data that could be used to carry out the Population 4 MAICs and reweighted IPD analyses:

- NATALEE trial (IPD) - ribociclib+AI and AI data
- monarchE trial[12] (aggregate data) - abemaciclib+ET and ET data.

Key characteristics of the monarchE trial[12] are provided in Table 13.

Table 13 Key characteristics of the monarchE trial

Trial parameter	monarchE trial[12] (N=5120)[a]
Design	• Ongoing, phase III, multi-centre, international, open-label, randomised controlled trial • 603 centres across 38 countries: Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Czech Republic, Denmark, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Israel, Italy, Japan, Republic of Korea, Mexico, Netherlands, New Zealand, Poland, Portugal, Puerto Rico, Romania, Russia, Saudi Arabia, Singapore, South Africa, Spain, Sweden, Taiwan, Turkey, Ukraine, UK and US

Population	• Patients (≥18 years) with HR-positive, HER2-negative, node-positive, early breast cancer at a high-risk of recurrence
	• Resected invasive early breast cancer without metastases and randomised ≤16 months post-surgery
	• ECOG PS 0 to 1
	Cohort 1 (n=5120)
	• Pathological tumour involvement in:
	  • ≥4 positive ALNs, or
	  • 1 to 3 positive ALNs, and at least one of the following criteria:
	  • grade 3 disease (defined as ≥8 points on the modified Bloom–Richardson grading system or equivalent), or
	  • primary tumour size ≥5cm.
	Cohort 2 (n=517)
	• Pathological tumour involvement in 1 to 3 ALNs and Ki-67≥20%

Intervention	• Abemaciclib 150mg BID continuously for ≤24 months AND • ET (tamoxifen, toremifene, letrozole anastrozole or exemestane, with or without ovarian suppression) for 5 to 10 years
Comparator	• ET (tamoxifen, toremifene, letrozole anastrozole or exemestane, with or without ovarian suppression) for 5 to 10 years
Primary outcome	• iDFS
Secondary outcomes	• DRFS, OS, PROs (EQ-5D-5L FACT-B, FACT-ES, FACIT- F), safety and pharmacokinetics/pharmacodynamics
Data presented in CS	• Data cutoff: July 2023

[a] Only patients in Cohort 1 of the monarchE trial[12] meet the eligibility criteria for treatment with abemaciclib, as per the NICE recommendation (TA810)[9]
ALN=axillary lymph node; BID=twice per day; CS=company submission; DRFS=distant relapse-free survival; ECOG PS=Eastern Cooperative Oncology Group performance status; EQ-5D-5L=EuroQol-5 Dimensions-5 Levels; ET=endocrine therapy; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; FACT-B=Functional Assessment of Cancer Therapy-Breast; FACT-ES=Functional Assessment of Cancer Therapy-Endocrine Subscale; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; IA3=interim analysis 3; iDFS=invasive disease-free survival; OS=overall survival; PROs=patient-reported outcomes
Source: Johnston 2023[22]

The company only included monarchE trial[12] Cohort 1 clinical effectiveness evidence in the company MAICs and reweighted IPD analyses. The TA810[9] NICE Appraisal Committee noted that the abemaciclib marketing authorisation[23] was only granted for monarchE trial[12] Cohort 1 patients and concluded that monarchE trial[12] Cohort 1 clinical effectiveness evidence was generalisable to NHS patients.

3.4.2 Quality assessment of the monarchE trial

The company assessed (CS, Appendix D.10, Table 23) the quality of the monarchE trial[12] using the quality assessment checklist for RCTs[17] devised by the CRD at the University of

York The company's assessments and EAG comments are presented in Table 14. The EAG's assessment is that the monarchE trial[12] is of good methodological quality.

Table 14 Quality assessment for the monarchE trial

Quality assessment item	Risk of bias		EAG comment
	Company	EAG	
Was the randomisation carried out appropriately?	Low	Low	Block randomisation was stratified and completed using IWRS
Was the concealment of treatment allocation adequate?	Low	Low	Block randomisation was stratified and completed using IWRS
Were the groups similar at the outset of the study in terms of prognostic factors?	Low	Low	Clinical advice to the EAG is that the baseline characteristics of patients in the monarchE trial[12] Cohort 1 (CS, Table 32) were well-balanced across the treatment arms
Were the care providers, participants and outcome assessors blind to treatment allocation?	High	Unclear	The monarchE trial[12] is open-label and outcomes were investigator-assessed. However, the secondary outcome, OS, is an objective measure and therefore is not subject to bias. iDFS, DRFS and safety may be subject to investigator and/or evaluation bias
Were there any unexpected imbalances in drop-outs between groups?	Low	Low	Discontinuations were well-balanced across the abemaciclib+ET (510/2794, 18.3%) and the ET arms (485/2797, 17.3%)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low	Low	Pre-specified outcomes were reported
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Low	Low	Analyses included an ITT analysis; no missing data were imputed

CS=company submission; DRFS=distant relapse-free survival; EAG=External Assessment Group; ET=endocrine therapy; iDFS=invasive disease-free survival; ITT=intention-to-treat; IWRS=interactive web-based response system; OS=overall survival
Source: CS, Appendix D.10, Table 23; Johnston 2023[22]

3.4.3 Summary of the company MAIC and reweighted IPD analysis approaches

A summary and EAG critique of the statistical approaches used by the company to conduct the MAICs and reweighted IPD analyses are provided in Appendix 1, Section 8.1, Table 49.

3.4.4 Characteristics of the indirect comparison populations

A summary of monarchE trial[12] Cohort 1 and NATALEE trial Population 4 baseline characteristics is presented in Appendix 2, Section 8.2.2, Table 50.

Compared to the monarchE trial[12] Cohort 1 population, the NATALEE trial Population 4 included:

- [redacted] of patients based in North America/Europe (ribociclib+AI=[redacted], AI=[redacted]; abemaciclib+ET=[redacted], ET=[redacted]

- [redacted] patients with invasive ductal breast carcinoma (ribociclib+AI=[redacted], AI=[redacted]; abemaciclib+ET=[redacted], ET=[redacted]) and invasive lobular breast carcinoma (ribociclib+AI=[redacted], AI=[redacted]; abemaciclib+ET=[redacted], ET=[redacted]), but [redacted] of patients with tubular breast cancer (ribociclib+AI=[redacted], AI=[redacted]; abemaciclib+ET=[redacted], ET=[redacted])
- [redacted] of patients with tumour size <2cm (ribociclib+AI=[redacted], AI= [redacted]; abemaciclib+ET=[redacted], ET=[redacted])
- [redacted] of patients with tumour size ≥5cm (ribociclib+AI=[redacted], AI=[redacted]; abemaciclib+ET=[redacted], ET=[redacted])
- [redacted] of patients with Ki-67 index ≥20 (ribociclib+AI=[redacted], AI=[redacted]; abemaciclib+ET=[redacted], ET=[redacted]).

3.4.5 Company ITC methodology and EAG critique

The company conducted MAICs for two time-to-event (TTE) outcomes (iDFS and OS; NATALEE trial and monarchE[22] trial pre-defined endpoints) and five Grade ≥3 TEAEs (alanine transaminase [ALT] increased, diarrhoea, leukopenia, lymphopenia and neutropenia).

As the NATALEE trial and the monarchE trial[12] do not share a common comparator (patients in the control arms are treated with different therapies), it was not possible to form a connected network and, therefore, the company conducted unanchored MAICs to derive weighted Kaplan-Meier (K-M) curves and corresponding HRs using a method-of moments approach described in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18.[24] The EAG agrees that it was not possible to form a connected network.

MAIC: For the comparison of ribociclib+AI versus abemaciclib+ET, the company selected patients in the NATALEE trial ribociclib+AI and AI arms who met monarchE trial[12] Cohort 1 inclusion criteria (for more details, see Appendix 2, Section 8.2.1). The company then weighted NATALEE trial Population 4 ribociclib+AI IPD to match monarchE trial[12] Cohort 1 abemaciclib+ET arm baseline patient characteristics (aggregate-level data).

Reweighted IPD analysis: For the comparison of ribociclib+AI versus ET (company response to clarification question A6), the company selected patients in the NATALEE trial ribociclib+AI and AI arms who met monarchE trial[12] Cohort 1 inclusion criteria (for more details, see Appendix 2, Section 8.2.1). Baseline characteristics of patients in the NATALEE trial ribociclib+AI and AI arms were then weighted to match monarchE trial[12] Cohort 1 abemaciclib+ET and ET arms, respectively (aggregate-level data). The EAG considers that this analysis is not strictly an indirect comparison as it only utilises outcome data from NATALEE trial; despite matching to monarchE trial[12] summary patient characteristics, it is an

analysis of weighted NATALEE trial Population 4 ribociclib+AI and AI IPD.

Prognostic factors and treatment effect modifiers

The company recognises that an unanchored comparison relies on strong assumptions, including the assumption that all potential prognostic factors and treatment effect modifiers are accounted for and included in the model (i.e., there are no unobserved prognostic factors or effect modifiers). The company's primary adjusted model included 19 factors (Table 15) that measured patient baseline demographics and disease characteristics. The appropriateness of these factors was validated by company clinical experts. The company also performed univariate analyses to explore the prognostic ability of these factors. The EAG considers that the approach used by the company to select factors was appropriate and agrees with the company that inclusion of a broad set of patient characteristics mitigates the risk of residual confounding, which may undermine the robustness of MAIC results. The company also performed sensitivity analyses; these excluded four factors (sex, race, ethnicity and region).

Clinical advice to the EAG is that the prognostic factors and treatment effect modifiers included in the unanchored MAICs primary and sensitivity analyses were appropriate.

Matching using a large number of factors can lead to the following issues:

- the possibility of multicollinearity (i.e., two or more variables are highly correlated)
- when many factors have two to four levels, data may be sparse.

The company did not perform any assessment of correlation or any sensitivity analyses to explore the effect of adjustment using a parsimonious set of baseline patient demographics and disease characteristics. Therefore, the effects of multicollinearity, reducing the set of factors on uncertainty around MAIC and reweighted IPD analysis results and the effective sample sizes (ESS), are not known. The EAG however, considers that it is important to retain factors contributing unique information in the matching process to mitigate and reduce the risk of residual confounding, which may limit the robustness of unanchored comparison results.

Table 15 Prognostic factors and treatment effect modifiers included in the company MAICs

Prognostic factors and treatment effect modifiers	
MAIC and reweighted IPD analysis	**Sensitivity MAIC**
Age, sex, race, ethnicity, weight, BMI, geographical region, pathological diagnosis term, hormone receptor status, menopausal status, positive ALNs, histopathology at diagnosis, Ki-67 index, ECOG PS, TNM stage, tumour side, tumour size, prior chemotherapy and prior radiotherapy	The following factors were excluded: sex, race, ethnicity and region

Source: CS, Table 30
ALN=axillary lymph node; BMI=body mass index; CS=company submission; ECOG PS=Eastern Cooperative Oncology Group performance status; Ki-67= antigen Kiel-67; TNM= tumour-node-metastasis

Proportional hazards

iDFS and OS MAIC HRs for the comparison of ribociclib+AI versus abemaciclib+ET and versus ET were calculated using Cox proportional hazards (PH) regression modelling. The Cox PH model is only appropriate when there is no violation of the PH assumption. The company presented Schoenfeld residual plots and associated p-values from the primary MAIC (company response to clarification question A10, Figure 16 and Figure 17) for the comparison of ribociclib+AI versus abemaciclib+ET and concluded that the PH assumption was not violated for iDFS or OS.

Effective sample size

The weights obtained from the company's MAIC analyses were incorporated into a Cox regression model to provide an estimate of comparative efficacy both prior to and after weighting. Standard errors (SE) for logHRs for ribociclib+AI versus abemaciclib+ET and versus ET were based on robust sandwich estimators or bootstrapping for MAIC-weighted patients. The EAG agrees with the company that this method was appropriate.

The company assessed the performance of the primary MAIC by exploring the distribution of the weights and the ESS post-weighting (Table 16).

Table 16 NATALEE 5,101

trial Population 4: primary MAIC

	Ribociclib+AI	AI
Population 4 size	[redacted]	[redacted]
Effective sample size	[redacted]	[redacted]
Reduction in sample size	[redacted]	[redacted]

CS=company submission; MAIC=matching-adjusted indirect comparison
CS, Table 31

The company stated (CS, Section B.2.8.4, p94) that since the ESS values were relatively large after weighting, use of the MAIC that adjusted for all available characteristics was appropriate. However, the EAG highlights that a low ESS relative to the original sample size might be an indication that the weights are variable, potentially due to a lack of population overlap between NATALEE trial IPD and monarchE trial[12] aggregate-level data and this may render comparative efficacy and safety results unstable.[25]

Immature data

The iDFS and OS MAICs were populated with immature K-M data; median iDFS and OS were [redacted], and 3-year iDFS and OS rates were [redacted] in

both NATALEE trial Population 4 and the monarchE trial[12] Cohort 1; immature survival data may result in implausible estimates of survival benefit.

Time varying MAIC approach

The original company PH assessment results (CS, Appendix D.9.1) suggested that the PH assumption might not be valid. Therefore, the EAG requested (clarification question A10) that the company performed a time-varying MAIC approach for iDFS, adding a covariate in the Cox regression model for the interaction of treatment effect and time. Time-varying HR iDFS and OS MAIC results are presented in Section 3.4.6.

However, updated company PH assessment results (company response to clarification question A10) showed that the PH assumption was not violated for the company iDFS and OS MAICs for the comparison of ribociclib+AI versus abemaciclib+ET.

Simulated treatment comparison (STC)

Due to concerns about the substantial reduction in the post-weighted ESS, the EAG asked the company to carry out STCs (clarification question A9). The STC approach uses predictive equations to estimate the relationship between outcomes and selected prognostic factors and effect modifiers. The company explored the effect of using an accelerated failure time (AFT) regression model (Weibull distribution fitted to NATALEE trial Population 4 IPD), which included adjustment for identified prognostic characteristics measured at baseline; the company stated that these were the factors included in the MAICs. The company's STCs involved calculating an adjustment factor based on differences between average NATALEE trial and monarchE trial[12] baseline characteristics, and Weibull regression model parameter estimates. This adjustment factor was applied to NATALEE trial TTE data to create adjusted TTE data. These adjusted data, along with reconstructed monarchE trial[12] data, were used in a Cox PH regression model to calculate the HR for the comparison of ribociclib+AI versus abemaciclib+ET. The EAG considers the company's STC to be appropriate. Company iDFS and OS STC results are provided in Section 3.4.6.

Grade ≥3 TEAE MAIC results

The company used logistic regression to estimate Grade ≥3 TEAE rate odds ratios (ORs). The company stated that a continuity correction was applied where no events were observed in one or more treatment arms, although it is unclear if a continuity correction was required for any of the five TEAEs assessed in the MAIC. Abemaciclib+ET TEAE rate data were collected from the monarchE trial[22] safety population (i.e., pooled Cohort 1 and Cohort 2 data); the company licence for abemaciclib does not extend to monarchE trial[22] Cohort 2 patients (TA810[9]); however, clinical advice to the EAG is that AE rates are not likely to differ between

Cohort 1 and Cohort 2.

3.4.6 Indirect treatment comparison results

iDFS MAIC results

The company presented iDFS MAIC results for the comparison of ribociclib+AI versus abemaciclib+ET and the iDFS reweighted IPD analysis results for the comparison of ribociclib+AI versus ET; these results were generated using Population 4 TTE data (MAIC analysis: CS, Section 2.8.5; MAIC sensitivity analysis: CS, Appendix D.9.2). Key iDFS MAIC results are presented in Table 17 ; an HR<1.0 favours ribociclib+AI (i.e., there is a reduced risk of an iDFS event for patients treated with ribociclib+AI versus the comparator).

Table 17 iDFS MAIC and reweighted IPD analysis results (Population 4)

Comparison	Before matching, unweighted comparison HR (95% CI)	Primary analysis	Sensitivity analysis
		After matching, HR (95% CI)	After matching, HR (95% CI)
Ribociclib+AI vs abemaciclib+ET (MAIC)	[redacted]	[redacted]	[redacted]
Ribociclib+AI vs ET (reweighted IPD)[a]	[redacted]	[redacted]	[redacted]

[a] NATALEE trial AI data were used to inform the efficacy of ET in the comparison of ribociclib+AI versus ET
[b] Data extracted from company response to clarification question A2, Table 1; iDFS for the comparison of ribociclib+AI vs AI was reported as HR [redacted] (95% CIs [redacted] to [redacted]), p=[redacted] in CS, Table 33
AI=aromatase inhibitor; CI=confidence interval; CS=company submission; HR=hazard ratio; iDFS=invasive disease-free survival; IPD=individual patient-level data; MAIC=matching-adjusted indirect comparison
Source= CS, Table 33 and Appendix D.9.2, Table 20; company response to clarification question A2, Table 1

The company presented NATALEE trial ribociclib+AI and AI K-M data (prior to and after weighting) and monarchE trial[12] abemaciclib+ET K-M data for the MAIC primary analysis (CS, Section 2.8.5, Figure 25 and Figure 26) and the MAIC sensitivity analysis (CS, Appendix D.9.2, Figure 7 and Figure 8).

OS MAIC results

OS MAIC results are presented in Table 18; an HR value <1.0 favours ribociclib+AI (i.e., there is a reduced risk of death for patients treated with ribociclib+AI versus the comparator).

Table 18 OS MAIC and reweighted IPD analysis results (Population 4)

Comparison	Before matching, unweighted comparison HR (95% CI)	Primary analysis After matching, HR (95% CI)	Sensitivity analysis After matching, HR (95% CI)
Ribociclib+AI vs abemaciclib+ET (MAIC)	[redacted]	[redacted]	[redacted]
Ribociclib+AI vs ET (reweighted IPD)[a]	[redacted]	[redacted]	[redacted]

[a] NATALEE trial AI data were used to inform the efficacy of ET in the comparison of ribociclib+AI versus ET
[b] Data extracted from company response to clarification question A2, Table 4; OS for the comparison of ribociclib+AI vs AI was reported as HR [redacted] (95% CIs [redacted] to [redacted]), p=[redacted] in CS, Table 34
AI=aromatase inhibitor; CI=confidence interval; CS=company submission; HR=hazard ratio; MAIC=matching-adjusted indirect comparison; OS=overall survival
Source: CS, Table 34 and Appendix D.9.2, Table 21; company response to clarification question A2, Table 4

The company presented NATALEE trial ribociclib+AI and ET K-M data (prior to and after weighting) and monarchE trial[12] abemaciclib+ET K-M data for the MAIC primary analysis (CS, Section 2.8.5, Figure 27 and Figure 28) and the MAIC sensitivity analysis (CS, Appendix D.9.2, Figure 10 and Figure 11).

Grade ≥3 TEAE MAIC results

The company presented Grade ≥3 TEAEs MAIC results for the comparison of ribociclib+AI versus abemaciclib+ET. Results from the primary MAIC and the MAIC sensitivity analysis are presented in the CS (Section B.2.8.5 and Appendix D.9.2, respectively).

A summary of the ORs and associated 95% CIs (estimated using logistic regression) for the primary MAIC and MAIC sensitivity analyses are presented in Table 19; an OR value <1.0 favours ribociclib+AI (i.e., there are reduced odds of the TEAE under observation occurring in patients treated with ribociclib+AI versus abemaciclib+ET).

Compared with abemaciclib+ET, both prior to and after matching, ribociclib+AI was associated with statistically significantly reduced odds of Grade ≥3 diarrhoea, leukopenia, and lymphopenia, and statistically significantly increased odds of Grade ≥3 increased ALT and neutropenia. However, the EAG notes that whilst the company only matched NATALEE trial Population 4 data with monarchE trial[12] Cohort 1 (N=2555) data, monarchE trial[22] safety population outcome data (i.e., data from Cohort 1 and Cohort 2; N=2791) were used to inform the five TEAE MAICs.

Table 19 Grade ≥3 TEAE MAIC results: ribociclib+AI versus abemaciclib+ET (Population 4)

Outcome	Unweighted OR (95% CI)[a]	Primary MAIC analysis Weighted OR (95% CI)[a]	Sensitivity MAIC analysis Weighted OR (95% CI)[a]
ALT increased	[redacted]	[redacted]	[redacted]

Outcome	Unweighted OR (95% CI)[a]	Primary MAIC analysis Weighted OR (95% CI)[a]	Sensitivity MAIC analysis Weighted OR (95% CI)[a]
Diarrhoea	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]

[a] The company stated that "95% credible intervals (CrI) for the primary MAIC analysis comparison of TEAEs are shown" (CS, Section 2.8.5, p105); however, the EAG considers that the uncertainty around MAIC results is represented by 95% CI and not 95% CrI (which is consistent with the measure of uncertainty estimated in the iDFS and OS MAIC results), as the company has not described any MAICs within a Bayesian framework
AI=aromatase inhibitors; ALT=alanine transaminase; CI=confidence interval; CrI=credible interval; CS=company submission; ET=endocrine therapy; iDFS= invasive disease-free survival; MAIC=matching-adjusted indirect comparison; OR=odds ratio; OS=overall survival; TEAE=treatment-emergent adverse event
Source: CS, Table 35; and Appendix D.9.2, Table 22

iDFS STC result

The company iDFS STC analysis result for the comparison of ribociclib+AI versus abemaciclib+ET (Population 4) is presented in Table 20; for this comparison, the STC HR estimate is consistent with the MAIC HR.

The company presented Population 4 ribociclib+AI K-M data (prior to and after adjustment) and monarchE trial[12] abemaciclib+ET K-M data (company response to clarification question A9, Figure 13).

Table 20 iDFS STC result (Population 4)

Analysis	HR (95% CI)	p-value
Ribociclib+AI vs abemaciclib+ET	[redacted]	[redacted]

AI=aromatase inhibitor; CI=confidence interval; iDFS=invasive disease-free survival; ET=endocrine therapy; HR=hazard ratio; STC=simulated treatment comparison
Source: company response to clarification question A9, Table 14

DRFS STC result

The company also presented a distant recurrence-free survival (DRFS) STC result and concluded that the HR for the comparison of ribociclib+AI versus abemaciclib+ET was consistent with the iDFS HRs. Due to the absence of monarchE trial[12] DDFS data, the company was unable to perform a DDFS MAIC; however, the company considers that DRFS data are a close proxy for DDFS data (company response to clarification question A9).

Table 21 DRFS STC result (Population 4)

Analysis	HR (95% CI)	p-value
Ribociclib+AI vs abemaciclib+ET	[redacted]	[redacted]

AI=aromatase inhibitor; CI=confidence interval; DRFS=distant recurrence-free survival; ET=endocrine therapy; HR=hazard ratio; STC=simulated treatment comparison
Source: company response to clarification question A9, Table 16

OS STC result

The company OS STC results for the comparison of ribociclib+AI versus abemaciclib+ET (Population 4) analysis is presented in Table 22; for this comparison, the STC HR estimate is not consistent with the MAIC OS HR. The STC result is based on an adjustment factor obtained from fitting a Weibull model to the NATALEE trial IPD; the EAG recognises that this result may be sensitive to the choice of parametric distribution.

Population 4 ribociclib+AI K-M data (prior to and after adjustment) and abemaciclib+ET K-M data are presented as part of the company's response to clarification question A9.

Table 22 OS STC results (Population 4)

Analysis	HR (95% CI)	p-value
Ribociclib+AI vs abemaciclib+ET	[redacted]	[redacted]

AI=aromatase inhibitor; CI=confidence interval; ET=endocrine therapy; HR=hazard ratio; OS=overall survival; STC=simulated treatment comparison
Source: company response to clarification question A9, Table 15

iDFS time-varying HR MAIC results

The company iDFS time-varying HR MAIC results for the comparison of ribociclib+AI versus abemaciclib+ET are presented in Table 23. The coefficient for the interaction term was not statistically significant. This suggests that the iDFS HR does not vary with time; this is in line with the company conclusions that the PH assumption may be appropriate (company response to clarification question A10).

Table 23 iDFS time-varying HR MAIC results (Population 4)

iDFS	Estimate (SE)	HR (95% CI)
Treatment effect (ribociclib+AI vs abemaciclib+ET)	[redacted]	[redacted]
Treatment effect * time interaction (months)	[redacted]	[redacted]

CI=confidence interval; HR=hazard ratio; iDFS=invasive disease-free survival; SE=standard error
Source: company response to clarification question A10, Table 17

As the company concluded that, for OS and DDFS, the PH assumption was not violated, the company did not conduct OS or DDFS time-varying HR MAIC results (company response to clarification question A10).

3.4.7 ITC conclusions

For Population 4, the company conducted unanchored iDFS, OS and Grade ≥3 TEAE MAICs for the comparison of ribociclib+AI versus abemaciclib+ET and reweighted IPD analyses for the comparison of ribociclib+AI versus ET.

The EAG highlights that the company MAICs and STCs are unanchored comparisons; unanchored comparisons rely on the strong assumption of conditional constancy of absolute

effects, and therefore, results of comparative efficacy and safety may be biased by residual confounding, the extent of this potential bias is unknown.

Ribociclib+AI versus abemaciclib+ET

The EAG considers that the company MAIC and STC methods were generally appropriate. The EAG notes that the OS STC results are statistically significant whereas the OS MAIC results are not statistically significant. However, the company iDFS STC results are consistent with the company iDFS MAIC results. The EAG considers that the company's STC results may be more reliable than the company MAIC results as the STC approach incorporates a large number of prognostic factors and treatment effect modifiers without being impacted by a reduction in ESS.

Ribociclib+AI versus ET

The EAG considers that the company reweighted IPD analyses comparing the clinical effectiveness of ribociclib+AI versus ET are not strictly ITCs as they only utilise outcome data from the NATALEE trial; baseline characteristics of patients in the NATALEE trial ribociclib+AI and AI arms were weighted to match monarchE trial[12] Cohort 1 abemaciclib+ET and ET arms, respectively (aggregate-level data). The company's approach of weighting IPD provides an estimate of comparative efficacy within the monarchE trial[12] population, however, a limitation of this approach, is a reduction in post-weighting ESS which may result in more uncertain estimates of the treatment effect.

The EAG's preferred ITC results for the comparison of ribociclib+AI versus ET are the before matching, unweighted IPD results. The EAG cautions that these results have been generated using data from patients who **are** eligible for treatment with abemaciclib+ET. In the NHS, most patients who are eligible for treatment with abemaciclib+ET would be treated with abemaciclib+ET, not ET. The EAG considers that Population 5 is the most relevant population for the comparison of ribociclib+AI versus ET because all NHS patients who **are not** eligible for treatment with abemaciclib+ET would be treated with ET.

3.5 NATALEE trial Population 1 patient reported outcomes

In the NATALEE trial, HRQoL data were collected using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire breast cancer module (EORTC QLQ-BR23), EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) and the Hospital Anxiety and Depression Scale (HADS).

The company presented NATALEE trial Population 1 EORTC QLQ-C30 physical functioning sub-scale and EQ-5D-5L visual analogue scale (VAS) score results in the CS (Section 2.5.4). The company also provided (CS, Appendix N.1.3) EORTC QLQ-C30 global health score (GHS), EORTC QLQ-C30 emotional functioning scores, EORTC QLQ-C30 social functioning score, EORTC QLQ-BR23 breast symptom scores and HADS anxiety and depression score results for Population 1. All PRO results are from the IA3 11 January 2023 DCO;[19] patient report outcomes (PROs) were not assessed at the PA 21 July 2023 DCO[18] or the most recent 29 April 2024 DCO.[11]

Key NATALEE trial Population 1 PRO results are presented in Table 24.

.

Table 24 NATALEE trial PRO results

Patient reported outcome	EAG summary
EORTC QLQ-C30	
Physical functioning	The EAG agrees with the company (CS, p76) that across timepoints, the mean EORTC QLQ-C30 physical functioning scores were [redacted] between treatment arms (CS, Table 23) and that mean EORTC QLQ-C30 physical functioning scores [redacted] in both treatment arms over time
Emotional functioning	Mean EORTC QLQ-C30 emotional functioning scores were [redacted] between treatment arms and [redacted] over time (CS, Appendix N.1.3, Table 76 and Figure 29)
Social functioning	Mean EORTC QLQ-C30 social functioning scores were [redacted] between treatment arms and [redacted] over time (CS, Appendix N.1.3, Table 77 and Figure 30)
GHS	Mean EORTC QLQ-C30 GHS data show a [redacted] from baseline in [redacted]; the [redacted] in the ribociclib+AI arm was [redacted] than in the AI arm (CS, Appendix N.1.3, Table 75 and Figure 28)
EORTC QLQ-BR23 breast symptom	Mean EORTC QLQ-BR23 breast symptom scores were [redacted] between treatment arms and [redacted] over time [redacted] (CS, Appendix N.1.3, Table 78 and Figure 31)
EQ-5D-5L VAS	The EAG agrees with the company (CS, p79) that mean EQ-5D-5L VAS were [redacted] [redacted] and [redacted] baseline over time (CS, Table 24 and Figure 17)
HADS	
Anxiety	Mean HADS anxiety scores were [redacted] and [redacted] baseline over time (CS, Appendix N.1.3, Table 79 and Figure 32)
Depression	Mean HADS depression scores were [redacted] and [redacted] over time in [redacted] (CS, Appendix N.1.3, Table 80 and Figure 33)

EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-BR23=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire breast cancer module; EQ-5D-5L=EuroQol-5 Dimensions-5 Levels; GHS=global health score; HADS=Hospital Anxiety and Depression Scale; PRO=patient-reported outcome; VAS=visual analogue scale

3.6 NATALEE trial Population 1 safety and tolerability results

NATALEE trial Population 1 safety results are summarised in Section 3.6.1 to Section 3.6.3. Median duration of ribociclib treatment was [redacted] months (range: [redacted] months) and overall median duration of treatment was [redacted] months (range: [redacted] months) in both treatment arms (CSR 29 April 2024 DCO,[11] Table 4-1 and Table 4-2).

3.6.1 Treatment-emergent adverse events

Nearly all patients ([redacted], [redacted]) in the ribociclib+AI arm and most patients ([redacted], [redacted]) in the AI arm experienced ≥1 treatment-emergent adverse event (TEAE) of any grade. The most common any grade TEAEs (reported by ≥20% of patients) in the ribociclib+AI arm (CS, Table 38) were [redacted] ([redacted], [redacted]), arthralgia (979/2526, 38.8%), [redacted] ([redacted], [redacted]), nausea (594/2526, 23.5%), headache (579/2526, 22.9%), fatigue (575/2526, 22.8%), [redacted] ([redacted], [redacted])and [redacted] ([redacted], [redacted]). In the AI arm, only arthralgia (1083/2441, 44.4%) and hot flushes ([redacted], [redacted]) were reported by ≥20% of patients.

More patients in the ribociclib+AI arm experienced ≥1 Grade 3 TEAEs ([redacted], [redacted]) and/or Grade 4 TEAEs ([redacted], [redacted]) than in the AI arm ([redacted], [redacted] and [redacted], [redacted], respectively; CS, Table 38). The most common Grade 3 TEAEs in the ribociclib+AI arm were [redacted] ([redacted],

[redacted]) and [redacted]_([redacted], [redacted]), and the most Grade 4 TEAEs were [redacted] ([redacted], [redacted]) and [redacted] ([redacted], [redacted]). In the AI arm, the most common Grade 3 TEAE was [redacted] ([redacted], [redacted]).

More patients in the ribociclib+AI arm ([redacted], [redacted]) discontinued treatment and/or required dose interruptions ([redacted], [redacted]) due to AEs than in the AI arm ([redacted], [redacted]_and [redacted], [redacted], respectively; CS, Table 36).

3.6.2 Adverse events of special interest

More patients in the ribociclib+AI arm ([redacted], [redacted]) experienced adverse events of special interest (AESIs) than in the AI arm ([redacted], [redacted]; CS, Table 40). The most common AESIs (incidence ≥20%) in the ribociclib+AI arm were neutropenia (1587/2526, 62.8%), infections ([redacted], [redacted]), hepatobiliary toxicity (675/2526, 26.7%) and leukopenia ([redacted], [redacted]), and the most common AESI in the AI arm was infections ([redacted], [redacted]).

Clinical advice to the EAG is that QT interval prolongation is an AE of particular concern for treatment with ribociclib; patients who receive treatment with ribociclib+AI require additional electrocardiogram (ECG) monitoring. In the ribociclib+AI arm, 5.4% (136/2556) patients experienced QT interval prolongation compared to 1.6% (38/2441) patients in the AI arm.

3.6.3 Deaths

[redacted] patients died due to AEs in the ribociclib+AI arm ([redacted], [redacted]) than in the AI arm ([redacted], [redacted]; CS, Table 41). In the ribociclib+AI arm, most AE-related deaths were due to [redacted] ([redacted], [redacted]) or [redacted] ([redacted], [redacted]).

3.7 Summary and clinical effectiveness conclusions

The company provided clinical effectiveness evidence for the comparison of ribociclib+AI versus AI from the NATALEE trial, an ongoing, phase III RCT; the EAG considers that the NATALEE trial is a well-conducted trial of good methodological quality.

3.7.1 Direct clinical evidence

For Population 1, Population 4 and Population 5, the NATALEE trial results showed that compared with AI, treatment with ribociclib+AI statistically significantly improved iDFS, RFS and DDFS. However, the differences in iDFS, RFS and DDFS event rates between the ribociclib+AI and AI arms were modest. For Population 1, overall, HRQoL outcomes were [redacted] between treatment arms and either [redacted] or [redacted] over time.

The NATALEE trial ITT population (Population 1) includes patients who, if treated in the NHS, would be eligible for abemaciclib+ET (Population 4; TA810[9]) and patients who would be

ineligible for abemaciclib+ET (Population 5). Focusing on the NATALEE trial ITT population is problematic as the trial comparator is AI; most NHS patients who are eligible for treatment with abemaciclib+ET would be treated with abemaciclib+ET.

3.7.2 Indirect clinical evidence: population 4 (patients eligible for abemaciclib+ET)

The company conducted:

- unanchored iDFS, OS and Grade ≥3 TEAE MAICs for the comparison of ribociclib+AI versus abemaciclib+ET
- unanchored iDFS, DRFS (as a proxy for DDFS) and OS STCs for the comparison of ribociclib+AI versus abemaciclib+ET
- iDFS and OS reweighted IPD analyses for the comparison of ribociclib+AI versus ET.

Clinical advice to the EAG is that NATALEE trial Population 4 patients and monarchE trial[12] Cohort 1 patients are representative of NHS patients who are eligible for treatment with ribociclib+AI and abemaciclib+ET.

Ribociclib+AI versus abemaciclib+ET

The iDFS MAIC, iDFS STC and DRFS STC HR point estimate results are close to 1 and CIs include 1. The OS MAIC HR results showed that, compared to abemaciclib+ET, ribociclib+AI numerically improved OS; only the OS STC result was statistically significant. Of all the ITC approaches considered by the company, the EAG considers that the STC approach was the most robust. The EAG only requested (clarification question A9) STC results for the comparison of ribociclib+AI versus abemaciclib+ET (Population 4). This is a minor concern as Population 5 is the most representative of NHS patients who would be treated with ET and direct trial evidence for the comparison of ribociclib+AI versus AI is available from the NATALEE trial.

The Grade ≥3 TEAE MAICs showed that compared with abemaciclib+ET, ribociclib+AI was associated with statistically significantly reduced odds of Grade ≥3 diarrhoea, leukopenia, and lymphopenia, and statistically significantly increased odds of Grade ≥3 increased ALT and neutropenia.

Ribociclib+AI versus ET

The iDFS and OS reweighted IPD analyses showed that, compared with ET, treatment with ribociclib+AI statistically significantly improved iDFS and numerically improved OS (CIs include 1). However, the EAG highlights that the AI arm of the NATALEE trial was used to inform the efficacy of ET in the reweighted IPD analyses.

3.7.3 Safety conclusions

Clinical advice to the EAG is that ribociclib+AI is tolerable and that the AEs associated with ribociclib+AI are manageable in NHS clinical practice.

4 COST EFFECTIVENESS EVIDENCE

This section provides a summary of the economic evidence submitted by the company in support of the use of ribociclib+AI for the adjuvant treatment of HR-positive HER2-negative early breast cancer at high risk of recurrence. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has provided an electronic copy of their economic model, which was developed in Microsoft Excel.

4.1 Critique of the methods of review(s)

The company conducted three SLRs designed to identify relevant economic evaluations, utilities studies, and cost and resource use studies. The target population was patients with HR-positive/HER2-negative early breast cancer; there was no restriction on treatment.

Searches were originally conducted on 17 April 2023 and updated on 20 October 2023 and 1 July 2024. The original database searches were not limited by date. The company also searched conference proceedings (2021 to July 2024) and documents submitted to Health Technology Assessment (HTA) agencies. Full details of the company's SLR methods and results are presented in the CS (Appendix G [cost effectiveness], Appendix H [HRQoL] and Appendix I [cost and health care resource use]).

In the company's review of economic evaluations, 854 (original SLR: 710, October 2023 update: 58, July 2024 update: 86) unique papers and abstracts were identified via database searches. In the company's review of utility studies, 267 (original SLR: 215, October 2023 update: 20, July 2024 update: 32) unique papers and abstracts were identified via database searches. In the company's review of cost and resource use studies, 1634 (original SLR: 1216, October 2023 update: 133, July 2024 update: 285) unique papers and abstracts were identified via database searches.

Overall, 16 studies (reported in 22 records) were included across the company's three SLRs. Of these, 11 studies were published economic evaluations and five were published HTA reports. No studies evaluating the cost effectiveness of ribociclib+AI in patients with HR+/HER2– EBC were identified.

4.2 EAG critique of the company's literature review

The EAG considers the methods used to conduct the company's systematic review of cost effectiveness evidence were of a good standard.

Table 25 EAG appraisal of systematic review methods

Review process	EAG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	See CS, Appendix G.3, Table 29
Were appropriate sources searched?	Yes	See CS, Appendix G.2
Was the timespan of the searches appropriate?	Yes	See CS, Appendix G.2 Sources were searched from database inception
Were appropriate search terms used?	Yes	See CS, Appendix G.2, Table 25 to Table 27
Were the eligibility criteria appropriate to the decision problem?	Yes	See CS, Appendix G.3, Table 29
Was study selection applied by two or more reviewers independently?	Yes	See CS, Appendix G.3
Was data extracted by two or more reviewers independently?	Yes	See CS, Appendix G.3 One reviewer extracted data, and these data were checked by a second (independent) reviewer
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	N/A[a]	
Was the quality assessment conducted by two or more reviewers independently?	N/A[a]	
Were attempts to synthesise evidence appropriate?	N/A[a]	

[a] The company did not identify any economic evaluations that assessed the cost effectiveness of ribociclib+AI vs the relevant comparators for patients with HR-positive, HER2-negative early breast cancer.
CS=company submission; EAG=External Assessment Group; HER2=human epidermal growth factor receptor 2; HR=hazard ratio; N/A=not applicable
Source: LR*i*G in-house checklist

4.2.1 EAG conclusion

The company did not identify any relevant cost effectiveness studies as a result of the systematic review. Overall, the EAG is satisfied that the company has not missed any relevant economic studies.

4.2 EAG summary and critique of the company's submitted economic evaluation

4.2.1 NICE Reference Case checklist and Drummond checklist

The EAG appraisal of the company's economic analyses using the NICE Reference Case checklist and Drummond checklist is presented in Table 26 and Table 27.

Table 26 NICE Reference Case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Defining the decision problem	The scope developed by NICE	The company has not provided cost effectiveness for the group of patients who are not eligible for abemaciclib+ET; this is a relevant patient group. However, the EAG acknowledges that this subgroup was not specified in the final scope issued by NICE.
Comparators	As listed in the scope developed by NICE	The company has provided cost effectiveness results for the comparison of ribociclib+AI versus ET and versus abemaciclib+ET.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and 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
Synthesis of evidence on health effects	Based on systematic review	Yes
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 and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
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

EAG=External Assessment Group; EQ-5D=EuroQol 5 dimensions; NHS=National Health Service; NICE=National Institute for Health and Care; PSS=Personal Social Services; QALY=quality adjusted life year

Source: EAG assessment of NICE Reference Case[26]

Table 27 Critical appraisal checklist for the economic analysis completed by the EAG

Question	Critical appraisal	EAG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Partial	Results not available for Population 5 (i.e., only patients not eligible for treatment with abemaciclib+ET)
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Partial	Adverse events were poorly costed. Some utility values were lower than would be expected for NHS patients.
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	No	Modelled overall survival estimates were not presented or discussed

EAG=External Assessment Group; ET=endocrine therapy; NHS=National Health Service
Source: EAG assessment using Drummond and Jefferson checklist[27]

4.3 Model structure

The company developed a de novo semi-Markov model in Microsoft® Excel to evaluate the cost effectiveness of ribociclib+AI for the adjuvant treatment of HR-positive, HER2-negative early breast cancer. The model incorporates a de novo partitioned survival sub-model to generate outcomes for one of the included health states. The company model includes six mutually exclusive health states: iDFS, second primary malignancy (SPM), non-metastatic recurrence (NMR) remission, distant recurrence (DR), and death. The iDFS health state is split into two mutually exclusive sub-states: on-treatment and off-treatment. The DR health state is split into two mutually exclusive sub-states: ET-resistant and ET-sensitive.

All patients enter the model in the iDFS health state; in this health state patients are at risk of moving to the SPM health state, the NMR health state, the DR health state or the death health state. Patients in the NMR health state are at risk of moving to the remission health state or

the death health state. Patients in the remission health state are at risk of moving to the DR health state or the death health state. Patients enter the DR health state in the DR: progression free health state. Patients in the DR progression free health state can move to the DR: progressed disease health state or death. Patients in the DR: progressed disease health state can move to the death health state. The SPM health state and death health state are absorbing health states, so patients do not leave these states once entered.

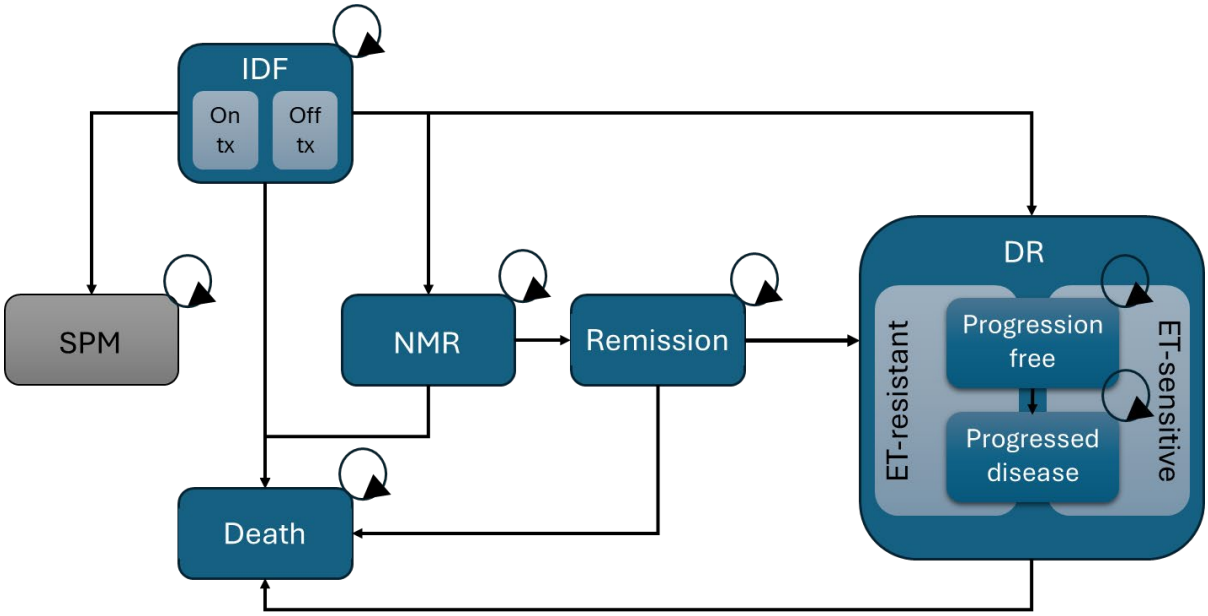


Figure 1 Simplified schematic of the model structure used in the cost utility analyses

DR=distant recurrence; ET=endocrine therapy; IDF=invasive disease-free survival; NMR=non-metastatic recurrence; SPM=second primary malignancy
Source: CS, Figure 29 (adapted to include iDFS on/off-treatment sub-states and DR progression free/progressed disease sub-states)

4.4 Population

The anticipated marketing authorisation extension is ribociclib in combination with an aromatase inhibitor (AI) for the adjuvant treatment of adult patients with hormone receptor (HR) positive (+)/human epidermal growth factor receptor 2 (HER2) negative (–) early breast cancer (EBC) at high risk of recurrence (CS, Table 2). The company has provided cost effectiveness results (company clarification response, Appendix) for the following NATALEE trial subgroups:

- Population 1 (ITT population; versus ET)
- Population 2 (node-positive high-risk population; versus ET)
- Population 3 (node-negative high-risk population; versus ET)
- Population 4A (unweighted node-positive high-risk eligible for abemaciclib; versus abemaciclib+ET)
- Population 4B (weighted node-positive high-risk eligible for abemaciclib; versus ET)

4.5 Interventions and comparators

4.5.1 Intervention

The modelled intervention is treatment with ribociclib+AI.

The ribociclib dose used in the company model is 400mg (two 200mg tablets) administered QD for 21 days followed by 7 days off treatment (28-day cycle overall); this approach is in line the NATALEE trial. Patients may continue ribociclib treatment until disease progression, unacceptable toxicity or for a maximum of 36 months.

The modelled AI treatment is a basket of therapies, namely anastrozole (1mg administered orally QD), letrozole (2.5mg administered orally QD) and exemestane (25mg administered orally QD). All the AI treatments are administered daily, i.e., without a break. Patients may continue AI treatment (as part of ribociclib+AI) until disease progression, unacceptable toxicity or for a maximum of 60 months.

In addition to ribociclib and an AI, some patients are modelled to receive add-on therapies: gonadotropin hormone-releasing hormone (GnRH) goserelin (3.6mg administered subcutaneously on day 1 of a 28-day cycle), and bisphosphonate zoledronic acid (4mg administered orally on day 1 of a 6-month cycle).

The proportions of patients receiving each AI therapy and add-on therapies were derived from NATALEE trial ribociclib+AI data and adjusted based on feedback from UK clinical experts collected during an advisory board (see CS, Appendix Q.3).

4.5.2 Comparators

For Population 1, Population 2 and Population 3, the comparator is ET. The modelled ET treatment is a basket of therapies, namely anastrozole (1mg administered orally QD), letrozole (2.5mg administered orally QD), exemestane (25mg administered orally QD) and tamoxifen (20mg administered orally once daily). All the ET treatments are administered daily, i.e., without a break for up to 60 months.

The Population 4 comparators are abemaciclib+ET and ET. The abemaciclib dose used in the company analysis is 600mg (2x150mg tablets administered orally BID). This modelled dose and treatment regimen is in line with the licensed dosing regimen[23] and the monarchE trial.[12] Patients may continue treatment with abemaciclib until disease progression, unacceptable toxicity or for a maximum of 24 months, in line with the monarchE trial.[12]

The modelled ET treatment is a basket of therapies, namely anastrozole (1mg administered orally QD), letrozole (2.5mg administered orally QD daily), exemestane (25mg administered

orally QD) and tamoxifen (20mg administered orally QD). Patients may continue ET until disease progression, unacceptable toxicity or for a maximum of 5 years.

In addition to abemaciclib and/or ET, some patients also receive add-on therapies: GnRH goserelin (3.6mg administered SC on day 1 of a 28-day cycle), and bisphosphonate zoledronic acid (4 mg administered orally on day 1 of a 6-month cycle).

The proportions of patients receiving each ET and add-on therapies were derived from NATALEE trial ribociclib+AI data and adjusted based on feedback from UK clinical experts collected during an advisory board (see CS, Appendix Q.3).

4.6 Perspective, time horizon and discounting

The model perspective was reported as NHS and Personal Social Services (PSS). The model cycle length was 28 days, and a half-cycle correction was applied to health outcomes and costs to account for mid-cycle progressions. The model time horizon was 50 years, and costs and outcomes were discounted at a rate of 3.5% per annum.

4.7 Health state transition probabilities and health state occupancy

Health state occupancy per cycle for all health states in the semi-Markov portion of the model is calculated based on transition probabilities. Transition probabilities for patients remaining in the iDFS health state are derived from parametric curves fitted to iDFS K-M data. Transition probabilities for iDFS events moving from the iDFS health state to other health states are calculated as a proportion of the cycle hazard rate. Transition probabilities to and from all other alive health states (except within and out of the DR state) are taken from the literature. Transition probabilities into the death health state (except from the DR state) were assumed to be equal to the iDFS mortality rate or background mortality rate, whichever was higher. Health state occupancy for the DR state and death from the DR health state are calculated based on a partitioned survival approach.

4.7.1 iDFS health state: Populations 1, 2 and 3

For Populations 1, 2 and 3, iDFS health state transition probabilities are principally derived from NATALEE trial data. Probabilities for remaining in the iDFS health state for patients treated with ribociclib+AI and patients treated with ET are calculated based on hazard rates from a parametric curve fitted to NATALEE trial iDFS K-M data from the ribociclib+AI and AI arms respectively. The fitted iDFS curves using the NATALEE trial ribociclib+AI iDFS data are used in the model directly to estimate ribociclib+AI iDFS health state occupancy.

Health state occupancy for ET iDFS is estimated using the parametric curves fitted to the NATALEE trial AI iDFS K-M data adjusted by an HR from the literature to incorporate the

efficacy of tamoxifen into the basket of ET treatments (HR=1.10 for tamoxifen, HR=1 for all other treatments in the basket. Tamoxifen is weighted as 20% of ET treatments for Population 1 resulting in HR=1.01 in the base case to adjust the AI curve to represent ET treatment). Parametric curves used to estimate iDFS for treatment with ribociclib+AI and patients treated with ETI are exponential for Populations 1 and 2. Base case Population 3 parametric curves for patients treated with ribociclib+AI and patients treated with ET are restricted cubic spline loglogistic curves.

4.7.2 iDFS health state: Population 4

For Population 4, iDFS health state transition probabilities are derived from the company ITC. Transition probabilities for remaining in the iDFS health state for patients treated with ribociclib+AI are calculated using hazard rates from an exponential curve fitted to NATALEE trial iDFS K-M data. Transition probabilities for treatment with abemaciclib+ET are assumed to equal those for ribociclib+AI. The fitted iDFS curves using the company MAIC iDFS results are used in the model directly to estimate ribociclib+AI and abemaciclib+ET iDFS health state occupancy.

Transition probabilities for treatment with ET are derived from the company's ITCs and adjusted by an HR from the literature to incorporate the efficacy of tamoxifen into the basket of ET treatments (HR=1.10 for tamoxifen, HR=1 for all other treatments in the basket. Tamoxifen is weighted as 10% of ET treatments for Population 4 resulting in HR=1.01 to adjust the AI curve to represent ET treatment).

4.7.3 iDFS treatment effect waning

Treatment effect waning is applied to the ribociclib+AI iDFS parametric curves for each population and to the abemaciclib+ET iDFS parametric curve for Population 4 to represent a reduction in treatment benefit versus treatment with ET over time. Treatment effect waning is applied as a constant increase in the cycle hazard rate for ribociclib+AI and abemaciclib+ET iDFS from a user-defined starting cycle until the point where iDFS hazards are equal to the background hazard rate. In the base case and for each population, treatment effect waning for treatment with ribociclib+AI (and abemaciclib+ET) is implemented from 8 years and reaches the background hazard rate at around 25 years. The distribution of iDFS events in the ribociclib+AI and abemaciclib+ET arms linearly approaches the distribution for ET such that they are equal at the end of the waning period.

4.7.4 NMR, remission, SPM and death health states (all populations)

Transition probabilities out of the NMR and remission health states into other alive health states were derived from the literature or assumptions. Transition probabilities into the death

health state were assumed to be equal to the iDFS mortality rate or background mortality rate, whichever was higher. The NMR health state is a tunnel state in which patients spend 12 months before being moved to the remission health state. Patients in the NMR health state may remain within the NMR health state or die in each cycle but may not progress to the DR health state nor enter the SPM health state. The SPM and death health states are absorbing health states.

4.7.5 DR health state (all populations)

DR health state occupancy is calculated as a weighted average of two three-state partitioned-survival models (ET-resistant DR substate and ET-sensitive DR substate) for patients treated with several different subsequent treatments. Health state occupancy for patients who receive subsequent treatment with ribociclib is derived from partitioned survival curves (PFS and OS) fitted to MONALEESA-2[28] (ET-sensitive) and MONALEESA-3[29] (ET-resistant) trial data. Outcomes for patients who receive subsequent treatments other than ribociclib are estimated using published HRs[30] applied to the ribociclib curves.

4.7.6 Health-related quality of life

HRQoL data were collected from the NATALEE trial ITT population using the EQ-5D-5L questionnaire. These EQ-5D-5L data (April 2024 data cut) were mapped to EQ-5D-3L data using the Hernández Alava[31] algorithm and the Policy Research Unit in Economic Methods of Evaluation of Health and Care Interventions (EEPRU) dataset[32] to generate health state utility values. In the company model, health state utility values do not differ by treatment or by population. The health state utility values used in the company model are provided in Table 28.

Table 28 Health state utility values used in the company model

Health state	Utility estimate	Source
On-treatment iDFS	0.7620	NATALEE trial
Off-treatment iDFS	0.7367	NATALEE trial
Remission	0.7367	Assumption made in TA810[9]
NMR	0.6818	NATALEE trial
DR[a]	0.6190	NATALEE trial
ET-resistant DR PFS	0.6190	Assumed equal to DR and equal for ET-resistant and ET-sensitive substates
ET-resistant DR PPS	0.5755	Calculated by taking the ratio of the utility values estimated for the PFS and PPS health states used in previous appraisals[10,33] of ribociclib (based on MONALEESA-2[28] and MONALEESA-3[29] trial data) and applying that ratio to the utility value for the DR PFS health state estimated using NATALEE trial data
ET-sensitive DR PFS	0.6190	Assumed equal utility for ET-resistant and ET-sensitive substates[11]
ET-sensitive DR PPS	0.5944	Calculated by taking the ratio of the utility values estimated for the PFS and PPS health states used in previous appraisals[10,33] of ribociclib (based on MONALEESA-2[28] and MONALEESA-3[29] data) and applying that ratio to the utility value for the DR PFS state estimated using NATALEE trial data

[a] This health state utility value is not used directly in the company model; however, ET-resistant and ET-sensitive DR PFS health state utility values were assumed to equal the DR health state utility value
DR=distant recurrence; ET=endocrine therapy; iDFS=invasive disease-free survival; NMR=non-metastatic recurrence; PFS=progression-free survival; PPS=post-progression survival
Source: CS, Table 56

4.8 Resources and costs

4.8.1 Drug costs: iDFS health state

Acquisition costs

Ribociclib and abemaciclib are available to the NHS at a confidential discounted PAS price. The PAS prices for ribociclib, and list prices for all other drugs are used in the company base case. Full details of ribociclib, abemaciclib and ET acquisition costs (per cycle) are presented in the CS (CS, Table 58).

Time to treatment discontinuation

Time to treatment discontinuation (TTD) data are used to partition the iDFS health state into on- or off-treatment states.

For Population 1, Population 2 and Population 3, the company model was populated with NATALEE trial ribociclib TTD data; the maturity of the data meant that extrapolation was not necessary. For AI (in combination with ribociclib) and ET, parametric curves were fitted to the combination AI arm and AI arm NATALEE trial TTD K-M data respectively. For the

combination treatment, TTD for ribociclib and AI were estimated separately since patients in the NATALEE trial could continue treatment with AI after ribociclib treatment was discontinued.

For Population 4, TTD K-M data from the post-matching and weighted NATALEE-trial TTD K-M data were used directly to estimate ribociclib TTD data. For AI (in combination with ribociclib), parametric curves were fitted to post-matching and weighted NATALEE-trial TTD K-M data. Estimates of TTD for ET alone were estimated from parametric curves fitted to post-matching and weighted NATALEE-trial TTD K-M data for the AI alone arm. Abemaciclib TTD data were estimated using parametric curves fitted to digitised monarchE trial[12] cumulative incidence of treatment discontinuation for reasons other than recurrence, which had been calibrated to match a 30.6% discontinuation rate at 24 months (as reported in Rugo 2022[34]). Estimates of TTD for ET in combination with abemaciclib were assumed to be the same as for AI in combination with ribociclib.

Company base case approaches to modelling TTD and the maximum treatment duration for each treatment are shown in Table 29.

Table 29 Company base case time to treatment discontinuation

Population	Intervention/ comparator	Treatment	Base case TTD extrapolation	Max treatment duration[a]
Base case (Population 1 [NATALEE ITT])	Ribociclib+AI	Ribociclib	TTD K-M (NATALEE ITT)	3 years
		AI	Weibull (R)	5 years
	ET	ET	Weibull (R)	5 years
Population 4 (node-positive high-risk eligible for abemaciclib)	Ribociclib+AI	Ribociclib	TTD K-M (NATALEE trial data matched to monarchE trial[12] data)	3 years
		AI	Lognormal (R)	5 years
	Abemaciclib+ET	Abemaciclib	monarchE trial[12] digitised TTD K-M data[34]	2 years
		ET	Lognormal (R)	5 years
	ET	ET	Lognormal (R)	5 years

[a] Maximum treatment duration based on NATALEE trial and monarchE trial[12] and clinical advice (CS, Appendix Q.2, p401)
AI=aromatase inhibitor; ET=endocrine therapy; K-M=Kaplan-Meier; R=restricted; TTD=time to treatment discontinuation
Source: CS, Table 58

Drug wastage

Wastage is included for treatment with abemaciclib to account for down-dosing due to AEs. Wastage is also included for both ribociclib and abemaciclib to account for unused whole packs of medication.

Relative dose intensity

The company applied relative dose intensity (RDI) multipliers to all treatments in all modelled populations (CS, Table 58). The RDI multiplier applied when estimating the cost of ribociclib ([redacted]) was sourced from the NATALEE trial ITT population ribociclib+AI arm. The RDI

multipliers for AIs in combination with ribociclib were sourced from the NATALEE trial ITT population ribociclib+AI arm (anastrozole=[redacted], letrozole=[redacted] and goserelin=[redacted]) and assumptions (exemestane equal to anastrozole and letrozole, zoledronic acid=[redacted]). The RDI multipliers for ET were sourced from the NATALEE trial ITT population AI arm (anastrozole=[redacted], letrozole=[redacted], tamoxifen=[redacted] and goserelin=[redacted]) and assumptions (exemestane equal to anastrozole and letrozole, zoledronic acid=[redacted]). The RDI multipliers applied to treatment with ribociclib+AI and ET are the same for each modelled population.

The company estimated the RDI multiplier for treatment with abemaciclib for Population 4 ([redacted]) based on the expected proportion of patients with a treatment pause. Since abemaciclib is subject to flat pricing, a reduction in dose intensity would not impact the cost per dose. Cycle cost of abemaciclib in a flat dosing scenario would only be affected by treatment holds. In the absence of treatment hold data for abemaciclib, the company used treatment hold data for ribociclib from the NATALEE trial ITT population to estimate the RDI multiplier for abemaciclib. The company assumed that each treatment in the ET basket in combination with abemaciclib had a [redacted] RDI, based on TA810.[9]

4.8.2 Subsequent treatment costs

NMR health state

Patients entering the NMR state were assumed to receive ET (letrozole, anastrozole, exemestane or tamoxifen) in the same proportions as patients in the Population 1 iDFS health state (CS, Table 59).

DR health state

The proportion of patients receiving a basket of subsequent therapies in the pre-progression DR health states is provided in the CS (Table 59) and company response to clarification (Table 19 and Table 20). Dosing schedules and acquisition costs for each of the subsequent therapies is given in the CS (Table 60 and Table 61). Subsequent therapies received in the progressed disease DR health states are not explicitly modelled; instead, a monthly cost of £1,170 is applied based on the mid-point of the Committee's preferred assumptions in TA496[35] (£1,140 to £1,200).

Time to treatment discontinuation

Estimates of TTD for each subsequent therapy are used to partition the DR health state into on- or off-treatment states. For combination ribociclib treatment in the DR ET-sensitive and ET-resistant health states, TTD was estimated by fitting parametric curves to MONALEESA-2[28] and MONALEESA-3[29] trial TTD K-M data, respectively. For all other treatments, TTD was assumed to equal PFS.

4.8.3 Drug administration costs

Goserelin and zoledronic acid are the only drugs subject to administration costs. All other modelled treatments are oral therapies, which are assumed to incur a zero administration cost.

4.8.4 Terminal costs

A one-off cost (£5,268.76) was applied on death; this cost was sourced from NICE CG81[36] and inflated to 2023 prices.

4.8.5 Adverse event costs

The model includes Grade ≥3 all-cause AEs that occurred in at least 5% of patients for any of the intervention or comparators of interest (CS, Table 50). For Populations 1-4, AE incidence rates for ribociclib+AI and ET were based on event rates for the given population in the relevant arm of the NATALEE trial. For treatment with abemaciclib+ET for Population 4, incidence rates were based on data from the monarchE trial.[12] Unit costs for each AE were sourced from the NHS Cost Collection[37] (CS, Table 66). AE costs were applied per cycle across the full time horizon.

4.8.6 Health state costs and resource use

The health state resource use data used in the company model (CS, Table 64 and CS, Table 65) were sourced from TA612[38] and TA810,[9] with additional treatment-specific healthcare resources for follow-up and monitoring for ribociclib and abemaciclib included based on their information provided in the respective Summaries of Product Characteristics[6,23] (CS, Table 65).

4.9 Severity modifier

The company concluded that ribociclib+AI did not meet the NICE severity modifier criteria.

5 COST EFFECTIVENESS RESULTS

The company base case probabilistic results (1,000 model iterations) from the clarification model are presented in Table 30 (Population 1) and Table 31 (Population 4). Cost effectiveness results for all other populations are available in the CS. All results were generated using the PAS prices for ribociclib and alpelisib, and list prices for all other drugs.

Table 30 Company Population 1 base case probabilistic pairwise results (PAS prices for ribociclib and alpelisib, list prices for all other drugs): company clarification model

Treatment	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
ET	[redacted]	15.01	[redacted]				
Ribociclib plus AI	[redacted]	15.65	[redacted]	[redacted]	0.64	[redacted]	Dominant

AI=aromatase inhibitor; ET=endocrine therapy; ICER=incremental cost effectiveness ratio; LY=life year; PAS=Patient Access Scheme; QALY=quality adjusted life year
Source: company clarification response, Table 22

Table 31 Company Population 4 base case probabilistic results (PAS prices for ribociclib and alpelisib, list prices for all other drugs): company clarification model

Treatment	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Ribociclib+AI	[redacted]	15.46	[redacted]				
ET	[redacted]	14.67	[redacted]	[redacted]	-0.80	[redacted]	Dominated
Abemaciclib+ET	[redacted]	15.45	[redacted]	[redacted]	-0.02	[redacted]	Dominated

AI=aromatase inhibitor; ET=endocrine therapy; ICER=incremental cost effectiveness ratio; LY=life year; PAS=Patient Access Scheme; QALY=quality adjusted life year
Source: company clarification response, Table 31

5.1 Sensitivity analyses

In the CS, for Populations 1 to 4, the company varied parameter input values individually in deterministic sensitivity analyses (DSA). Upper and lower values were based on +/- 10% of the mean base case value.

Cost effectiveness results for the comparison of ribociclib+AI and ET for Populations 1 to 4 were most sensitive to parameters determining PFS and OS in the DR health state, and to the QALY discount rate (CS, Figure 41, Figure 45, Figure 49 and Figure 55). Cost effectiveness results for the comparison of ribociclib+AI and abemaciclib+ET for Population 4 were most sensitive to abemaciclib RDI and percentage of people receiving abemaciclib (CS, Figure 56). However, updated results are not presented in the company response to clarification.

5.2 Scenario analyses

The company conducted scenario analyses to explore the effect of alternative model assumptions on cost effectiveness results. Scenario analysis results (n=25) showed that, for Population 1, in all except three scenarios ribociclib+AI dominated treatment with ET. The three scenarios where ribociclib+AI was not dominant are shown in Table 32.

Table 32 Key company scenario analysis results (Population 1, clarification model)

Parameter	Alternative scenario	ICER per QALY gained
Population 1 (ribociclib+AI versus ET)		
Treatment waning	Effect assumed constant up to 5 years, with treatment waning from 5 to 8 years only	£5,647
Efficacy of post-progression therapies in the DR health state	ET-resistant MONALEESA-3 trial[29] OS: Weibull (restricted)	£2,903
Treatment mix (DR health state)	90% of patients in the ribociclib+AI arms received CDK4/6 rechallenge as per ET arm (ET-sensitive DR health state)	£2,033

AI=aromatase inhibitor; CDK4/6=cyclin dependent kinase 4/6; DR=distant recurrence; ET=endocrine therapy; ICER=incremental cost effectiveness ratio; OS=overall survival; QALY=quality adjusted life year
Source: company clarification response, Table 23

All the company Population 4 scenario analyses (n=27) carried out for the comparison of ribociclib+AI versus ET and for the comparison of ribociclib+AI versus abemaciclib+ET generated results that showed that treatment with ribociclib+AI was dominant (company clarification response, Table 30 and Table 32).

5.3 Model validation and face validity check

Technical validation of the model structure, inputs, calculations and face validity checks of results were carried out by an independent health economist.

External validation of the model structure, key inputs and assumptions utilised in the model, including treatment mixes and subsequent treatment choices, treatment efficacy assumptions and survival curve extrapolations were carried out by clinical experts in November 2023 and September 2024.

6 EAG CRITIQUE OF COMPANY ECONOMIC MODEL

The company model, developed in MS Excel, is designed to compare treatment with ribociclib+AI versus abemaciclib+ET and ribociclib+AI versus ET for patients with HR+/HER2- early breast cancer at high risk of recurrence. The EAG has checked that the parameter values in the CS match those used in the company model and were derived accurately from appropriate sources.

In response to the clarification letter, the company submitted a new model (referred to as company clarification model).

Clinical advice to the EAG is that patients who are not eligible for abemaciclib+ET are treated with ET regardless of the nodal status of their breast cancer. This means that Population 2 and Population 3 are less relevant to this appraisal than Populations 1, 4 and 5. The EAG has only generated cost effectiveness results for Population 1 (proxy for Population 5) and Population 4.

The EAG cautions that OS over time (including median OS) cannot be directly estimated from the model due to the approach used to calculate life years in the DR health state. Additionally, patients who transition into the SPM health state exit the model, and so their deaths are not included in the life years calculation and would not be included in any OS estimates. This means that the EAG has not been able to compare the OS estimates generated by the model with clinical advice or with long-term OS reported in the literature. Therefore, all model cost effectiveness results may not be robust. This issue is of particular concern for the comparisons of ribociclib+AI versus ET as, for the comparison of ribociclib+AI versus abemaciclib+ET, the company survival estimates for patients treated with these two treatments are almost identical.

6.1 Overview of modelling issues identified by the EAG

A summary of the EAG's critique of the company's cost effectiveness analyses is provided in Table 33.

Table 33 Summary of EAG company model critique

Aspect considered	EAG comment	Section of EAG report
Model structure	• The company model structure is generally appropriate but does not allow OS estimates to be calculated over time (including median OS) so these cannot be validated by the EAG. Additionally, patients who transition into the SPM health state exit the model, and so their deaths are not included in the life years calculation.	NA
Population	• The EAG considers that the focus of this appraisal should be on Population 4 and Population 5. As the company has not presented Population 5 cost effectiveness results, the EAG has used Population 1 cost effectiveness results as a proxy for Population 5 results.	6.2
Comparators	• The comparators considered by the company are ET and abemaciclib+ET. • The EAG considers that it is only appropriate to use Population 1 clinical effectiveness results to generate cost effectiveness results for the comparison of ribociclib+AI versus ET for patients who are not eligible for abemaciclib+ET (Population 5) as most NHS patients who are eligible for treatment with abemaciclib+ET will be treated with abemacicilib+ET. • The company has assumed that the efficacy of ET is the same as the efficacy of AI adjusted for lower expected efficacy of tamoxifen; for the purposes of the economic evaluation, clinical advice to the EAG is that this approach is reasonable.	6.2
Modelling iDFS	• The company used a semi-Markov approach to model iDFS transition probabilities for the comparison of ribociclib+AI versus ET, using parametric iDFS curves and proportions of different iDFS event types based on the results of the NATALEE trial. The iDFS data are immature. Published data are not available to help estimate long-term iDFS and therefore the EAG has not made any changes to the modelling of iDFS but cautions long-term iDFS is subject to uncertainty. • There is insufficient statistical evidence to suggest that the distribution of iDFS event types differs between ribociclib+AI and ET. The EAG has adjusted the iDFS event distribution for treatment with ET so that it matches the distribution for ribociclib+AI. • The company has assumed that the iDFS efficacy for ribociclib+AI and abemaciclib+ET for Population 4 is the same; the EAG is satisfied with this assumption based on company ITC results.	6.3.1 and 6.3.2
Treatment effect waning	• Treatment effect waning assumptions are included in the model but the evidence to support these assumptions is lacking. The EAG has presented alternative scenarios.	6.3.3

Aspect considered	EAG comment	Section of EAG report
Modelling DR	• Estimates of PFS and OS for treatments in the DR health state use HRs applied to accelerated failure time parametric curves. This approach is technically incorrect. The EAG has chosen alternative PFS and OS curves for ribociclib in the ET-resistant and ET-sensitive DR substates. • The company has not provided evidence for, or justified the assumption of, PHs for PFS and OS in the DR substates. This means that the use of HRs applied to the ribociclib reference curves may not be appropriate, and costs and benefits arising from treatments in the ET-resistant and ET-sensitive DR substates are uncertain.	6.4
Modelling OS	• It is not possible to estimate OS from the model because the payoff approach is used to estimate life years in the DR health state. The EAG cautions that OS has not been validated for this analysis.	6.0
Utility values	• The company has assumed that HRQoL will be the same for patients with DR regardless of the time of relapse. Clinical advice to the EAG is that ET-resistant patients are likely to have lower HRQoL than ET-sensitive patients due to differences in the aggressiveness of the disease. The EAG has adjusted utility values in the ET-sensitive DR substate to reflect this expectation.	6.4.4
Drug costs	• The EAG has no concerns about the company's drug costs.	NA
Subsequent treatment costs	• The proportion of CDK4/6 inhibitors included in the treatment baskets in the ET-resistant and ET-sensitive DR substates do not align with clinical advice to the company. The EAG has adjusted the weights in the ET-resistant and ET-sensitive treatment baskets to reflect clinical advice to the company.	6.4
Healthcare resource use	• The EAG has no concerns about the company's healthcare resource use costs.	NA
Adverse events	• The company has underestimated unit costs for the principal AEs included in the analysis. The EAG has altered these costs to reflect the severity of Grade ≥3 AEs.	6.5
Severity modifier	• The EAG agrees with the company that ribociclib+AI does not meet the NICE severity modifier criteria.	NA
PSA	• The EAG has no concerns about the company implementation of the PSA. • However, to allow for flexibility, the EAG used a Dirichlet distribution to sample the iDFS event distribution.	NA

AE=adverse event; AI=aromatase inhibitor; DR=distant recurrence; EAG=External Assessment Group; ET=endocrine therapy; HRQoL=health-related quality of life; HR=hazard ratio; ITC=indirect treatment comparison; ITT=intention to treat; NA=not applicable; NICE=National Institute for Health and Care Excellence; OS=overall survival; PFS=progression-free survival; PH=proportional hazards; PSA=probabilistic sensitivity analysis; QALYs=quality adjusted life years

6.2 Population

In the CS, the company has provided NATALEE trial clinical effectiveness evidence relating to four populations (Population 1, Population 2, Population 3 and Population 4). In response to clarification question A2, the company provided clinical effectiveness results for two further populations (Population 5 and Population 6). The EAG considers that Population 4 and

Population 5 are the most relevant populations for this appraisal. For a full discussion of the populations considered by the company, please see Section 2.4.6.

The company base case cost effectiveness analysis focuses on Population 1. Population 1 includes patients who would be eligible for abemaciclib+ET (Population 4; TA810[9]) and patients who would be ineligible for abemaciclib+ET (Population 5). The EAG considers that focusing on Population 1 is problematic as the comparator is ET alone; most NHS patients who are eligible for treatment with abemaciclib+ET would be treated with abemaciclib+ET and not ET alone.

The EAG considers that the focus of this appraisal should instead be on Population 4 and Population 5. As the company has not presented Population 5 cost effectiveness results, the EAG has generated cost effectiveness results for Population 5 using Population 1 clinical effectiveness data. This approach is in line with the company response to clarification question B1 where the company stated that "the efficacy of ribociclib+AI versus ET in [the NATALEE high-risk ineligible for the abemaciclib] population is aligned with that of the broader ITT population".

Since the company has not presented Population 5 cost effectiveness results, the Population 5 cost effectiveness results have been generated using Population 1 data. The EAG notes, therefore, that the Population 5 ICERs per QALY gained may be overestimated, i.e., Population 5 cost effectiveness results may be conservative.

6.3 iDFS health state

6.3.1 Survival modelling: iDFS

The company commented (CS, p152) that long-term iDFS data are lacking for a population consistent with the NATALEE trial, so iDFS curve selection was based on "visual fit and statistical goodness-of-fit, but primarily on clinical plausibility". All parametric distributions fitted by the company have similar face validity versus the trial K-M data and little to separate them using Akaike information criterion (AIC) and Bayesian information criterion (BIC) scores (Population 1: CS, Figure 31; Population 4: CS, Appendix R.1.4, Table 115). However, the set of candidate fitted curves vary substantially after the end of the trial data and for the remainder of the model time horizon (see Figure 2for an example).

The company chose to use the exponential distribution for ribociclib+AI, abemaciclib+ET and ET in both Population 1 and Population 4 since this distribution had the lowest BIC score in each case. The plausibility of the exponential curves was validated via clinical advice to the company.

The EAG undertook a pragmatic search of the literature to investigate whether there were any published long-term iDFS data that could be used to validate the company's projections in either Population 1 or Population 4. The EAG identified one study (Martin 2023)[39] that reported 5- and 10-year iDFS (75.2% and 57.0% respectively) for a population equivalent to Population 4 who had been treated with ET. The company's candidate ET curves are visually similar up to 10 years, and 10-year iDFS is within [redacted] of the 10-year iDFS rates reported by Martin 2023[39] for over half of the company's candidate curves (Figure 2). The candidate curves that were visually similar to those reported by Martin 2023[39] included the exponential curves. The candidate curves that were not similar to those reported by Martin 2023[39] had extreme high or low long-term ET iDFS estimates.

Figure 2 Company candidate fitted iDFS curves: ET, Population 4

Source: company clarification model

As published iDFS data are only available for 10 years, these data cannot be used to validate the company extrapolations beyond 10 years. Therefore, the EAG has not made any changes to the company base case iDFS curves for Population 1 or Population 4. Further, the EAG cautions that NATALEE trial iDFS data are immature and long-term iDFS estimates remain subject to substantial uncertainty.

6.3.2 Relative transition probabilities

Transition probabilities from the iDFS health state into each downstream health state are calculated as the risk of leaving the iDFS health state in each model cycle (using the iDFS curve) multiplied by the probability of moving from the iDFS health state into a given destination health state. For instance, the transition probability for moving from the iDFS health state into the death health state in cycle 2 is: $(1 - (iDFS_{t=3}/iDFS_{t=2})) * \%\ of\ events\ that\ are\ death$. The proportion of iDFS events that are non-metastatic recurrence (NMR), second primary malignancy (SPM), disease recurrence (DR) and death in the

company base case clarification model differ by treatment (Table 34) but are the same for Population 1 and Population 4.

Table 34 Proportions of NATALEE trial iDFS events

Analysis/ Treatment arm	Number of events	% iDFS events that are NMR (95% CI)	% iDFS events that are death (95% CI)	% iDFS events that are DR (95% CI)	% iDFS events that are SPM (95% CI)	% iDFS events Missing type (95% CI)
Ribociclib+AI[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] This distribution is also used for abemaciclib+ET for Population 4
AI=aromatase inhibitor; CI=confidence interval; DR=distant recurrence; ET=endocrine therapy; iDFS=invasive disease-free survival; NMR=non-metastatic recurrence; SPM=second primary malignancy
Source: company response to clarification question B5, Table 21

The EAG requested CIs around the point estimates used in the company model (clarification question B5) to assess whether the assumption of a relative treatment effect for iDFS event distribution was reasonable. In each health state, the 95% CIs for each treatment overlap substantially, indicating that there is insufficient statistical evidence of a difference between the iDFS event distributions based on treatment.

The EAG would have preferred that the iDFS event distributions were pooled across treatments so that iDFS event proportions were equal for treatment with ribociclib+AI and ET. In the absence of pooled iDFS event proportion estimates, the EAG has set the iDFS event proportions for all treatments to equal those for ribociclib+AI. The EAG highlights that this EAG revision does not result in equal transition probabilities (or equal efficacy) for the two treatments since the underlying probabilities of experiencing any iDFS event differ between the two treatments (Table 35). This aligns with clinical advice to the company that they would expect patients that receive ribociclib+AI to have a reduced proportion of DR and NMR events versus ET (company response to clarification question B8).

Table 35 iDFS cycle transition probabilities after EAG revision

Analysis/ Treatment arm	iDFS to iDFS	iDFS to NMR	iDFS to death	iDFS to DR	iDFS to SPM
Ribociclib+AI[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] This distribution is also used for abemaciclib+ET for Population 4
AI=aromatase inhibitor; DR=distant recurrence; ET=endocrine therapy; iDFS=invasive disease-free survival; NMR=non-metastatic recurrence; SPM=second primary malignancy
Source: company clarification model

6.3.3 iDFS treatment effect waning

The EAG considers that the company treatment effect waning assumption is arbitrary, highly uncertain and not supported by evidence. Varying the treatment waning assumption has a substantial impact on cost effectiveness results (CS, Table 74 and Table 89).

The company incorporated treatment effect waning assumptions for ribociclib+AI and abemaciclib+ET based on evidence of a "carryover benefit" noted in the ATAC trial[40] (CS, p161). ATAC trial[40] results indicated that the risk of recurrence continued to be lower for patients treated with anastrazole than for patients treated with tamoxifen even after treatment had finished, but that the size of the benefit began to decrease at by 8 years. The EAG considers that, since this evidence does not include outcomes for CDK4/6 inhibitor, it is not directly relevant to this appraisal. However, the EAG acknowledges that clinical advice to the company was that a "carryover benefit" followed by treatment effect waning was clinically plausible and that the carryover benefit might be expected to last for between 5 and 10 years (CS, p161).

In the company base case, the treatment effect waning period is set to end at the point where ribociclib+AI iDFS reaches general population mortality; that is, patients treated with ribociclib+AI (or abemaciclib+ET) are assumed to have a lower risk of recurrence than patients treated with ET alone until the point where they have no excess risk from breast cancer. Ribociclib+AI iDFS hazard rates are equal to general mortality rates at 25 years for Population 1 and equal to 27 years for Population 4. The EAG considers that these time points are arbitrary.

The EAG has presented two treatment effect waning scenarios: a) treatment effect waning is removed entirely and a constant iDFS treatment effect is assumed over the model time horizon and b) treatment effect is assumed to be constant from 0 to 5 years and then waned over years 5 to 8, after which iDFS transition probabilities are equal for ribociclib+AI (and abemaciclib+ET) and ET. These scenarios mirror those presented in the CS (Table 74, Table 89 and Table 90). Longer-term follow up data would allow iDFS to be robustly estimated using independent curves as well as by using PH or accelerated failure time models; then, treatment effect waning would be implicitly modelled.

6.4 Distant recurrence health state

6.4.1 ET-resistant and ET-sensitive PFS and OS

The company has used weighted baskets of treatments to estimate PFS and OS in the ET-resistant and ET-sensitive DR substates. The proportions of each treatment included in each basket differ according to adjuvant treatment received. The types of treatment included in each basket differ according to whether patients are considered to be ET-resistant or ET-sensitive. The treatment baskets are the same for all populations (CS, Appendix S.1, Table 119 and Appendix S.2, Table 124).

Outcomes (PFS and OS) for the treatment baskets were estimated by fitting parametric PFS and OS curves for ribociclib+fulvestrant (ET-resistant DR substate) or ribociclib+NSAI (ET-sensitive DR substate) to patient-level data from the MONALEESA-2[28]and MONALEESA-3[29] trials, respectively. Outcomes for other treatments in the baskets were estimated by applying HRs from a published network meta-analysis (NMA)[30] to the modelled ribociclib curves.

Varying PFS and OS for baskets of treatments in the ET-resistant and ET-sensitive DR substates has a substantial impact on cost effectiveness results for the comparison of ribociclib+AI versus ET. The EAG has two concerns about the company's base case approach to modelling PFS and OS for treatments in the ET-resistant and ET-sensitive substates:

- it is not appropriate to apply HRs to loglogistic (OS) and lognormal (PFS) curves
- the long-term PH assumptions have not been justified for the comparison of ribociclib+AI versus the basket of treatments

For ribociclib+AI in the ET-sensitive DR substate, the EAG has used the company post-progression efficacy scenario PFS (exponential) and OS (Gamma) curves (CS, Table 49).

For ribociclib+AI in the ET-resistant DR substate, the company post-progression efficacy scenario PFS curve (lognormal [U]) is not compatible with the PH assumption but the OS curve (Weibull [R]) is compatible with the PH assumption. The only one of the company's candidate PFS PH curves to retain a logical relationship with the company's post-progression efficacy scenario Weibull OS curve (i.e. PFS<OS at all times) is the exponential curve. Clinical advice to the EAG is that curves chosen by the EAG generate plausible long-term PFS and OS estimates for both DR substates.

The EAG alternative PFS and OS curves for the ET-sensitive and ET-resistant DR substates are presented in Table 36 alongside landmark PFS and OS estimates. The EAG alternative PFS and OS curves in both the ET-sensitive and ET-resistant DR substates substantially reduce the length of the long tails associated with the company base case curves (Figure 3 and Figure 4).

Table 36 Landmark ribociclib PFS and OS distributions in the DR health state (company and EAG alternative)

Health state	Outcome	Company/EAG	Distribution	Landmark efficacy[b]			
				5 years	10 years	20 years	30 years
ET-resistant	PFS	Company	Lognormal (R)	[redacted]	[redacted]	[redacted]	[redacted]
		EAG	Exponential	[redacted]	[redacted]	[redacted]	[redacted]
	OS	Company	Loglogistic (R)	[redacted]	[redacted]	[redacted]	[redacted]
		EAG	Weibull (R)[a]	[redacted]	[redacted]	[redacted]	[redacted]
ET-sensitive	PFS	Company	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
		EAG	Exponential[a]	[redacted]	[redacted]	[redacted]	[redacted]
	OS	Company	Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
		EAG	Gamma[a]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Indicates company scenario analysis distribution
[b] Including background mortality
EAG=External Assessment Group; DR=distant recurrence; ET=endocrine therapy; OS=overall survival; PFS=progression-free survival; R=restricted
Source: company clarification model

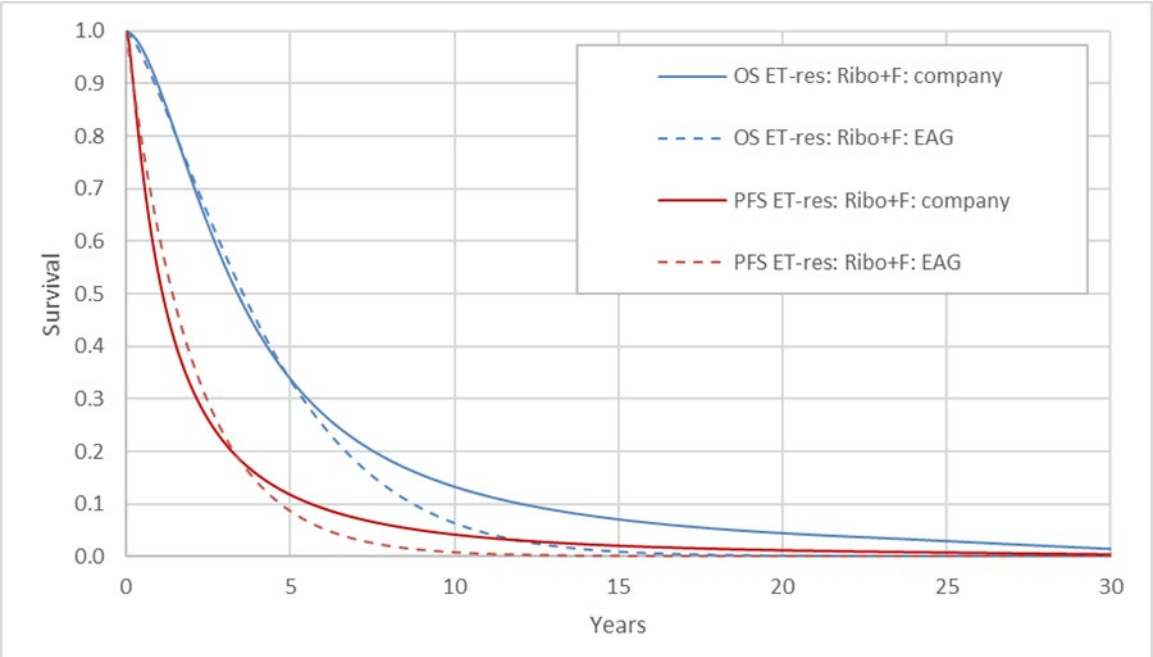


Figure 3 Company and EAG PFS and OS curves for the ET-resistant DR substate

ET=endocrine therapy; F=fulvestrant; OS=overall survival; PFS=progression-free survival; res=resistant; ribo=ribociclib
Source: company clarification model

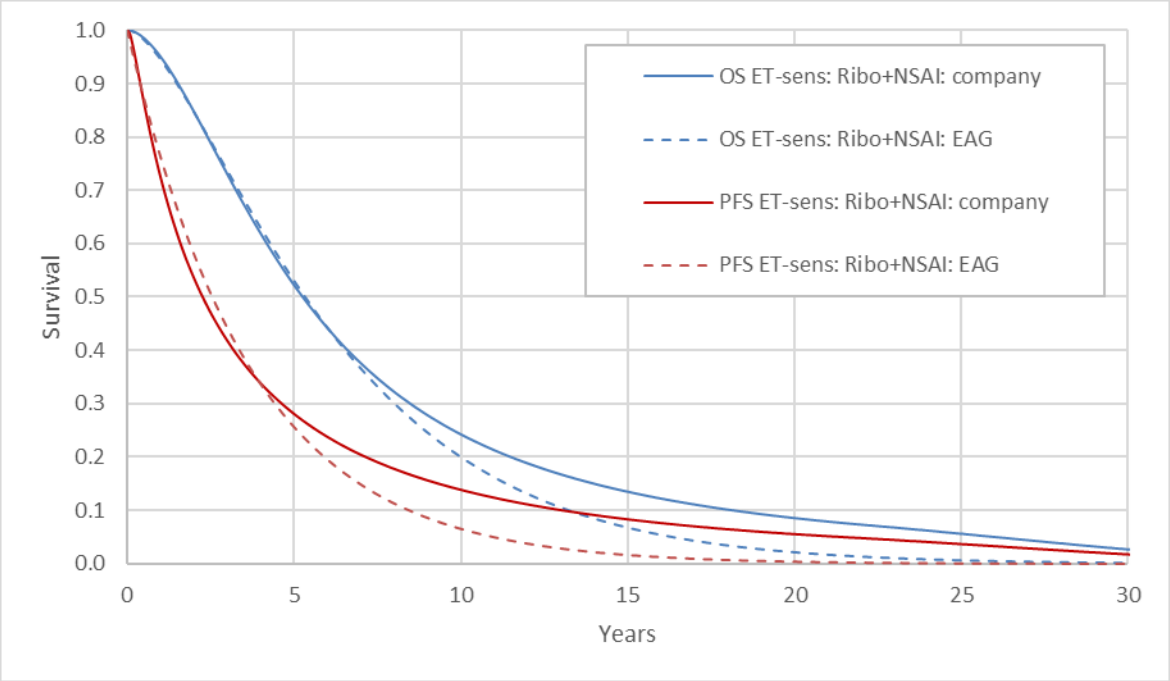


Figure 4 Company and EAG PFS and OS curves for the ET-sensitive DR substate

EAG=External Assessment Group; ET=endocrine therapy; NSAI=non-steroidal aromatase inhibitor; OS=overall survival; PFS=progression-free survival; ribo=ribociclib; sens=sensitive
Source: company clarification model

The EAG has not made any changes to the HRs used by the company to generate PFS and OS curves for non-ribociclib treatments. However, the EAG cautions that treatment benefits versus ribociclib in the ET-resistant and ET-sensitive DR substates are conferred for the whole model horizon as a result of using HRs to estimate outcomes for non-ribociclib treatments. The effect of the PH assumption being violated in the long-term for multiple treatments is uncertain and would have an unknown effect on model cost effectiveness results.

6.4.2 Treatment mix: ET-resistant DR substate

The proportion of ET-resistant, CDK4/6-sensitive patients who have been previously treated with a CDK4/6 inhibitor (ribociclib or abemaciclib) who are likely to receive a subsequent CDK4/6 inhibitor is uncertain. The majority of clinical advice to the company was that, although the NHS Blueteq form has been updated to allow retreatment of patients who received a CDK4/6 inhibitor in the adjuvant setting, it is too early to know how this change would impact prescribing since a CDK4/6 inhibitor (abemaciclib) has only been available in the adjuvant setting since 2022 (CS, Appendix Q.3, p414). One clinician considered that most eligible patients would be retreated with a CDK4/6 inhibitor whilst another considered that CDK4/6 inhibitor use would be lower for ET-resistant CDK4/6 inhibitor-sensitive patients than for patients who had received adjuvant ET alone. Another clinician considered that most patients would be retreated with a CDK4/6 inhibitor.

The company has assumed that 30% of ET-resistant, CDK4/6 inhibitor-sensitive patients would receive subsequent CDK4/6 inhibitor treatment (company response to clarification question B4, Table 19 and Table 20). This assumption aligns with the advice of one expert to the company that a lower proportion of ET-resistant CDK4/6 inhibitor-sensitive patients would be treated with a CDK4/6 inhibitor than patients who has received adjuvant ET alone.

The EAG has presented a scenario where 90% of ET-resistant CDK4/6 inhibitor-sensitive patients are retreated with a CDK4/6 inhibitor. In the EAG scenario, the proportion of ET-resistant CDK4/6 inhibitor-sensitive patients retreated with a CDK4/6 inhibitor is equal to the proportion of patients receiving a CDK4/6 inhibitor following adjuvant ET alone. This assumption aligns with the advice of one expert to the company that most patients would be retreated with a CDK4/6 inhibitor. The company and EAG treatment distributions in the ET-resistant DR substate are shown in Table 37.

Table 37 Subsequent treatment distribution: ET-resistant DR substate

DR Substate	CDK eligibility	Treatment	ET	Ribociclib+AI		Abemaciclib+ET	
			Company	Company	EAG	Company	EAG
ET-resistant	Resistant	Ribo+F	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Palbo+F	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Abema+F	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Eve+Exe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alpelisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ET-resistant	Sensitive	Ribo+F	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Palbo+F	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Abema+F	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Eve+Exe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alpelisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

abema=abemaciclib; AI=aromatase inhibitor; DR=distant recurrence; EAG=External Assessment Group; ET=endocrine therapy; eve=everolimus; exe=exemestane; F=fulvestrant; palbo=palbociclib; ribo=ribociclib
Source: company clarification model

6.4.3 Treatment mix: ET-sensitive DR substate

Clinical advice to the company (CS, Appendix Q.3, p414) was that the treatment distribution for ET-sensitive CDK4/6 inhibitor-sensitive patients treated with adjuvant CDK4/6 inhibitors would be the same as that for patients who received adjuvant ET alone. However, the company considered that this estimate was too high, given the uncertainty in prescribing subsequent therapy following treatment with adjuvant CDk4/6 inhibitors (company response to clarification question B4). Instead, the company assumed that 45% of ET-sensitive CDK4/6 inhibitor-sensitive patients who received adjuvant treatment with a CDK4/6 inhibitor would be

retreated with a CDK4/6 inhibitor when entering the ET-sensitive DR substate versus 90% of patients who receive adjuvant ET alone.

The EAG prefers the company's alternative scenario in which the proportion of patients retreated with a CDK4/6 inhibitor in the ET-sensitive DR substate is equal to the proportion of patients receiving a CDK4/6 inhibitor following adjuvant ET alone (90%). This scenario aligns with the treatment distribution estimates agreed at the company's September 2024 advisory board meeting (CS, Appendix Q.2, Table 112). The company and EAG treatment distributions in the ET-sensitive DR substate are shown in Table 38.

Table 38 Treatment distribution: ET-sensitive DR substate

DR Substate	CDK eligibility	Treatment	ET	Ribociclib+AI		Abemaciclib+ET	
			Company	Company	EAG	Company	EAG
ET-sensitive	Sensitive	Ribo+NSAI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Palbo+NSAI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Abe+NSAI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Letrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

abema=abemaciclib; AI=aromatase inhibitor; DR=distant recurrence; EAG=External Assessment Group; ET=endocrine therapy; eve=everolimus; exe=exemestane; F=fulvestrant; NSAI=non-steroidal anti-inflammatory; palbo=palobociclib; ribo=ribociclib
Source: company clarification model

6.4.4 Utility values

The modelled progression-free utility values are the same for both the ET-resistant DR substate and ET-sensitive DR substate, but the progressed disease utility values differ between the two substates. The company notes (and clinical advice to the EAG agrees) that ET-resistant disease is often more aggressive than ET-sensitive disease and would therefore be expected to be associated with lower HRQoL (company response to clarification question B3). However, clinical advice to the EAG is that HRQoL differs between ET-resistant and ET-sensitive disease from the time of relapse. This means that it would also be expected that the ET-resistant progression free utility value would be lower than the ET-sensitive progression free utility value.

Clinical advice to the EAG is that, in the absence of utility values specific to the ET-sensitive progression free substate, it is reasonable to set the ET-sensitive PFS utility value to equal the NMR health state utility value in order to differentiate progression free HRQoL between the ET-sensitive and ET-resistant substates. The EAG has therefore presented a scenario using the NMR health state utility value (derived from the NATALEE trial and used in the company base case) as the ET-sensitive PFS utility value. Progressed disease utility values in this scenario are calculated as a ratio of progressed disease to progression free utility values

from the MONALEESA-2 trial[28] and the MONALEESA-3 trial[29], as per the company base case. The company and EAG DR health state utility values are shown in Table 39.

Table 39 Company and EAG DR health state utility values

	Company		EAG	
DR substate	Progression free	Progressed disease	Progression free	Progressed disease
ET-resistant	[redacted]	[redacted]	[redacted]	[redacted]
ET-sensitive	[redacted]	[redacted]	[redacted]	[redacted]

DR=distant recurrence; EAG=External Assessment Group; ET=endocrine therapy
Source: company clarification model

6.5 Adverse event costs

The company clarification model includes Grade ≥3 AEs with incidence ≥5% in any treatment arm. Each AE is assumed to cost one medical oncology consultant appointment (£190.83). Since Grade ≥3 AEs indicate hospitalisation, the EAG has applied AE-specific costs that more accurately reflect severity and treatment costs (Table 40).

Table 40 Company base case and EAG AE unit costs

AE	**Company base case**		**EAG base case**	
	Unit cost	**Source**	**Unit cost**	**Source**
ALT increased	£190.53	NHS Reference Costs 22-23;[37] WF01A, Consultant Led, Medical Oncology Non-admitted Face to Face Attendance, Follow Up	£792	NHS Reference Costs 23-24;[41] Non-Elective Inpatient – Short Stay Unit Cost
Diarrhoea			£1975	NHS Reference Costs 23-24;[41] weighted average of codes FD10A-M by activity (Non-Elective Inpatient Long Stay, Non-Elective Inpatient short stay, Day case, and Regular Day or Night Admissions): Non-Malignant Gastrointestinal Tract Disorders with Multiple Interventions, with Single Intervention and without Intervention with CC Score 0-8+
Leukopenia			£1454	NHS Reference Costs 23-24;[41] Weighted average of codes SA08G-J by activity (Non-Elective Inpatient Long Stay, Non-Elective Inpatient short stay, Day case, and Regular Day or Night Admissions): Other haematological or splenic disorders with CC Score 0-6+
Lymphopenia			£1454	Assumed same as leukopenia
Neutropenia			£193	NHS Reference Costs 23-24;[41] WF01A Medical oncology (service code: 370) non-admitted face to face attendance follow up.

AE=adverse event; ALT=Alanine aminotransferase; CC=complex and comorbidity; EAG=External Assessment Group

6.6 Impact of EAG amendments on the company base case results

The EAG has generated cost effectiveness results (using the company clarification model) by making the revisions presented in Table 41. The company identified two errors in its modelling during the factual accuracy check process. These errors were rectified by the EAG and are included in the company FAC base case.

Table 41 EAG model revisions

EAG revisions
R1) Adjust proportion of patients moving from iDFS to other health states
R2) Choose alternative PFS and OS in DR state
R3) Adjust treatment mix in ET-resistant DR substate
R4) Adjust treatment mix in ET-sensitive DR substate
R5) Change ET-sensitive health state utility values
R6) Adjust AE unit costs
SI and S2) Alternative treatment waning scenarios

AE=adverse event; DR=distant recurrence; EAG=External Assessment Group; ET=endocrine therapy; iDFS=invasive disease-free survival; OS=overall survival; PFS=progression-free survival

Details of EAG revisions to the company model are presented in Appendix 8.3 of this EAG report. Deterministic cost effectiveness results for pairwise comparisons are provided in Table 43, Table 45 and Table 47. Probabilistic cost effectiveness results for pairwise comparisons are presented in Table 44, Table 46 and Table 48. All results have been generated using 2023 list prices for all drugs except for ribociclib and alpelisib (PAS price). All results tables have been replicated in the confidential appendix and the analyses include all confidential commercial arrangements as described in Table 42.

Table 42 Pricing sources used in the confidential appendix

Treatment	Price source/type of commercial arrangement
Ribociclib	PAS
Abemaciclib	PAS
Alpelisib	PAS
Palbociclib	PAS
Letrozole	eMIT
Anastrozole	eMIT
Exemestane	eMIT
Zoledronic acid	eMIT
Tamoxifen	eMIT
Everolimus	eMIT
Fulvestrant	eMIT
Paclitaxel	eMIT
Capecitabine	eMIT
Goserelin	BNF

British National Formulary; eMIT=electronic Market Information Tool; PAS=Patient Access Scheme
Source: price tracker form (November 2024)

Table 43 Deterministic pairwise results (ribociclib+AI versus ET, Population 1), PAS price for ribociclib and alpelisib

EAG revisions	Ribociclib+AI		ET		Incremental		ICER £/QALY	NMB (WTP=£30,000)
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A1. Company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**	**£15,896**
A2. Company FAC base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**	**£15,862**
R1) Adjust iDFS event distribution	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,800	£14,414
R2) Choose alternative PFS and OS in DR state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£967	£16,527
R3) Adjust treatment mix in ET-resistant DR substate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,116	£13,411
R4) Adjust treatment mix in ET-sensitive DR substate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,205	£14,325
R5) Change ET-sensitive health state utility values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£15,169
R6) Adjust AE unit costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£15,759
B1. EAG alternative base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£14,952**	**£9,269**
S1) B1+Treatment effect waning for ribociclib+AI: 5 to 8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,204	-£835
S2) B1+Remove treatment waning for ribociclib+AI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9,263	£14,705

AE=adverse events; AI=aromatase inhibitor; EAG=External Assessment Group; ET=endocrine therapy; ICER=incremental cost effectiveness ratio; iDFS=invasive disease-free survival; NMB=net monetary benefit OS=overall survival; PFS=progression-free survival; PAS=Patient Access Scheme; QALYs=quality adjusted life year; WTP=willingness to pay

Table 44 Probabilistic pairwise results (ribociclib+AI versus ET, Population 1), PAS price for ribociclib and alpelisib

EAG revisions	Ribociclib+AI		ET		Incremental		ICER £/QALY	NMB (WTP=£30,000)
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A2. Company FAC base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£16,155
B1. EAG alternative base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,030	£9,300

AI=aromatase inhibitor; EAG=External Assessment Group; ET=endocrine therapy; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; PAS=Patient Access Scheme; QALYs=quality adjusted life year; WTP=willingness to pay

Table 45 Deterministic pairwise results (ribociclib+AI versus abemaciclib+ET, Population 4*), PAS price for ribociclib and alpelisib

EAG revisions	Ribociclib+AI		Abemaciclib+ET		Incremental		ICER £/QALY	NMB (WTP=£30,000)
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A1. Company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**	**£44,127**
A2. Company FAC base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**	**£44,125**
R1) Adjust iDFS event distribution	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£44,125
R2) Choose alternative PFS and OS in DR state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£44,139
R3) Adjust treatment mix in ET-resistant DR substate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£43,955
R4) Adjust treatment mix in ET-sensitive DR substate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£44,125
R5) Change ET-sensitive health state utility values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£44,145
R6) Adjust AE unit costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£44,127
B1. EAG alternative base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**	**£44,266**
S1) B1+Treatment effect waning for ribociclib+AI: 5 to 8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£44,225
S2) B1+Remove treatment waning for ribociclib+AI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£44,266

*Model Population 4B
AE=adverse events; AI=aromatase inhibitor; EAG=External Assessment Group; ET=endocrine therapy; ICER=incremental cost effectiveness ratio; iDFS=invasive disease-free survival; NMB=net monetary benefit OS=overall survival; PFS=progression-free survival; PAS=Patient Access Scheme; QALYs=quality adjusted life year; WTP=willingness to pay

Table 46 Probabilistic pairwise results (ribociclib+AI versus abemaciclib+ET, Population 4*), PAS price for ribociclib and alpelisib

EAG revisions	Ribociclib+AI		Abemaciclib+ET		Incremental		ICER £/QALY	NMB (WTP=£30,000)
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A2. Company FAC base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£43,349
B1. EAG alternative base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£43,485

*Model Population 4B
AI=aromatase inhibitor; EAG=External Assessment Group; ET=endocrine therapy; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; PAS=Patient Access Scheme; QALYs=quality adjusted life year; WTP=willingness to pay

Table 47 Deterministic pairwise results (ribociclib+AI versus ET, Population 4*), PAS price for ribociclib and alpelisib

EAG revisions	Ribociclib+AI		ET		Incremental		ICER £/QALY	NMB (WTP=£30,000)
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A1. Company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**	**£22,875**
A2. Company FAC base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**	**£22,585**
R1) Adjust iDFS event distribution	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£21,416
R2) Choose alternative PFS and OS in DR state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£23,202
R3) Adjust treatment mix in ET-resistant DR substate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£19,930
R4) Adjust treatment mix in ET-sensitive DR substate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£20,953
R5) Change ET-sensitive health state utility values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£21,752
R6) Adjust AE unit costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£22,585
B1. EAG alternative base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£9,863**	**£15,748**
S1) B1+Treatment effect waning for ribociclib+AI: 5 to 8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,584	£3,088
S2) B1+Remove treatment waning for ribociclib+AI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,380	£21,943

*Model Population 4B
AE=adverse events; AI=aromatase inhibitor; EAG=External Assessment Group; ET=endocrine therapy; ICER=incremental cost effectiveness ratio; iDFS=invasive disease-free survival; NMB=net monetary benefit OS=overall survival; PFS=progression-free survival; PAS=Patient Access Scheme; QALYs=quality adjusted life year; WTP=willingness to pay

Table 48 Probabilistic pairwise results (ribociclib+AI versus ET, Population 4*), PAS price for ribociclib and alpelisib

EAG revisions	Ribociclib+AI		ET		Incremental		ICER £/QALY	NMB (WTP=£30,000)
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A2. Company FAC base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£21,924
B1. EAG alternative base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,548	£14,808

*Model Population 4B
AI=aromatase inhibitor; EAG=External Assessment Group; ET=endocrine therapy; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; PAS=Patient Access Scheme; QALYs=quality adjusted life year; WTP=willingness to pay

6.7 Conclusions of the cost effectiveness section

All cost effectiveness results presented in this report have been generated using PAS prices for ribociclib and alpelisib, and 2023 list prices for all other drugs.

For Population 4, in the company base case and in the EAG alternative base case, treatment with ribociclib+AI dominates treatment with abemaciclib+ET albeit due to a small increase in incremental QALYs associated entirely with assumptions about the efficacy of treatments in the DR health state. The EAG considers that the company assumption of equal efficacy between ribociclib+AI and abemaciclib+ET is supported by the results of the company iDFS ITCs and, based on the results of the OS STC, may even be a conservative estimate.

For Population 4, for the comparison of ribociclib+AI versus ET, the EAG alternative ICER per QALY gained lies between dominant and £23,584, depending on assumptions around treatment effect waning. The EAG highlights that most NHS patients suitable for treatment with abemaciclib+ET will be treated with abemaciclib+ET, and not ET.

The EAG has used Population 1 cost effectiveness results as a proxy for Population 5 cost effectiveness results. Depending on assumptions around treatment effect waning, the EAG alternative ICER per QALY gained for the comparison of ribociclib+AI versus ET, lies between dominant and £32,204. The EAG notes that iDFS HRs for Population 1 and Population 5 numerically favour Population 5, so using Population 1 data as a proxy for Population 5 data may be a conservative assumption.

The EAG considers that until model OS estimates over time (including median OS) can be compared with clinician estimates and published estimates, company and EAG cost effectiveness results may not be robust. The exclusion of deaths from second primary malignancies may prevent model OS outcomes being compared with OS from the literature or prespecified OS measures from the NATALEE trial. This issue is of particular concern for the comparisons of ribociclib+AI versus ET as, for the comparison of ribociclib+AI versus abemaciclib+ET, the company survival estimates for patients treated with these two treatments are almost identical.

7 REFERENCES

1. American Cancer Society. Breast Cancer Facts & Figures 2022-2024. Published 2022; Available from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/2022-2024-breast-cancer-fact-figures-acs.pdf. Accessed 22 November 2024.
2. NHS Digital. Cancer Registrations Statistics, England 2021- First release, counts only. Cancer incidence by stage. Published 19 October 2023; Available from: https://digital.nhs.uk/data-and-information/publications/statistical/cancer-registration-statistics/england-2021---summary-counts-only/cancer-incidence-by-stage. Accessed 22 November 2024.
3. Cancer Research UK. Survival for breast cancer. Published 8 June 2023; Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/survival#:~:text=Stage%201,with%20treatment%20for%20some%20years. Accessed 22 November 2024.
4. Early Breast Cancer Trialists' Collaborative Group. Reductions in recurrence in women with early breast cancer entering clinical trials between 1990 and 2009: a pooled analysis of 155746 women in 151 trials. The Lancet. 2024; 404:1407-18.
5. Rader J, Russell MR, Hart LS, Nakazawa MS, Belcastro LT, Martinez D*, et al.* Dual CDK4/CDK6 inhibition induces cell-cycle arrest and senescence in neuroblastoma. Clin Cancer Res. 2013; 19:6173-82.
6. Novartis. Data on File. Draft Ribociclib Annex I. Summary of producy characteristics. 2024.
7. European Medicines Agency. Kisqali. Procedural steps taken and scientific information after authorisation. Published 18 December 2024; Available from: https://www.ema.europa.eu/en/documents/procedural-steps-after/kisqali-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf. Accessed 6 February 2025.
8. National Institute for Health and Care Excellence. NG101. Early and locally advanced breast cancer: diagnosis and management. Published 16 January 2024; Available from: https://www.nice.org.uk/guidance/ng101/resources/early-and-locally-advanced-breast-cancer-diagnosis-and-management-pdf-66141532913605. Accessed 2 December 2024.
9. National Institute for Health and Care Excellence. Abemaciclib with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence. Technology appraisal guidance [TA810]. Published 20 July 2022; Available from: https://www.nice.org.uk/guidance/ta810. Accessed 26 November 2024.
10. National Institute for Health and Care Excellence. Ribociclib with an aromatase inhibitor for adjuvant treatment of hormone receptor-positive, HER2-negative early breast cancer [ID6153]. Final scope. Published 28 August 2024; Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta11090/documents. Accessed 14 November 2024.
11. Novartis. Data on File. NATALEE Clinical Study Report April 2024 data cut. 2024.
12. Rastogi P, O'Shaughnessy J, Martin M, Boyle F, Cortes J, Rugo HS*, et al.* Adjuvant abemaciclib plus endocrine therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative, high-risk early breast cancer: results from a preplanned monarchE overall survival interim analysis, including 5-year efficacy outcomes. J Clin Oncol. 2024; 42:987-93.
13. Paluch-Shimon S, Lueck H, Beith J, Tokunaga E, Contreras JR, Sant'Ana Rd*, et al.* 153P - Adjuvant endocrine therapy combined with abemaciclib in monarchE patients with high-risk early breast cancer: Disease characteristics and endocrine therapy choice by menopausal status. Ann Oncol. 2021; 32:S407-46.

14. National Institute for Health and Care Excellence. Olaparib for adjuvant treatment of BRCA mutation-positive HER2-negative high-risk early breast cancer after chemotherapy. Technology appraisal guidance [TA886]. Published 10 May 2023; Available from: https://www.nice.org.uk/guidance/ta886. Accessed 10 December 2024.
15. Hudis CA, Barlow WE, Costantino JP, Gray RJ, Pritchard KI, Chapman JA*, et al.* Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. J Clin Oncol. 2007; 25:2127-32.
16. National Institute for Health and Care Excellence. Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer. Clinical guidelines [CG164]. Published 14 November 2023; Available from: https://www.nice.org.uk/guidance/cg164. Accessed 29 November 2024.
17. Centre for Reviews and Dissemination. Systematic Reviews: CRD's guidance for undertaking reviews in health care. York: University of York 2008.
18. Novartis. Data on File. NATALEE Clinical Study Report primary pre-planned analysis of iDFS July 2023 data cut. 2023.
19. Novartis. Data on file. NATALEE Clinical Study Report January 2023 data cut. 2023.
20. Novartis. Data on File. NATALEE Protocol. Statistical Analysis Plan (15 August 2022); 327-83.
21. Novartis. Data on File. NATALEE Protocol. Clinical trial protocol version 4.0. 2020; 145-269.
22. Johnston SRD, Toi M, O'Shaughnessy J, Rastogi P, Campone M, Neven P*, et al.* Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. Lancet Oncol. 2023; 24:77-90.
23. European Medicines Agency. Abemaciclib. Annex I. Summary of Product Characteristics. Published 18 December 2024; Available from: https://www.ema.europa.eu/en/documents/product-information/verzenios-epar-product-information_en.pdf. Accessed 6 January 2024.
24. Phillippo D, Ades T, Dias S, Palmer S, Abrams KR, Welton N. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE. Published December 2016; Available from: https://www.sheffield.ac.uk/nice-dsu/tsds/full-list. Accessed 4 December 2024.
25. Phillippo DM, Dias S, Elsada A, Ades AE, Welton NJ. Population adjustment methods for indirect comparisons: a review of National Institute for Health and Care Excellence Technology Appraisals. Int J Technol Assess Health Care. 2019; 35:221-8.
26. National Institute for Health and Care Excellence. Health Technology Evaluations: The Manual. Process and Methods [PMG36]. Economic Evaluation. Published 31 January 2022; Available from: https://www.nice.org.uk/process/pmg36/chapter/economic-evaluation-2. Accessed 4 December 2024.
27. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ. 1996; 313:275-83.
28. 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. Ann Oncol. 2018; 29:1541-7.
29. Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA*, et al.* Overall Survival with Ribociclib plus Fulvestrant in Advanced Breast Cancer (MONALEESA-3). NEJM. 2019; 382:514-24.

30. Shao H, Zhao M, Guan A-J, Shao T, Zhou D, Yu G*, et al.* A network meta-analysis of efficacy and safety for first-line and second/further-line therapies in postmenopausal women with hormone receptor-positive, HER2-negative, advanced breast cancer. BMC Medicine. 2024; 22:13.
31. Hernandez-Alava M, Wailoo A, Pudney S. Methods for mapping between the EQ 5D 5L and the 3L for technology appraisal. Report by the Decision Support Unit report. Published 11 July 2017; Available from: https://www.sheffield.ac.uk/nice-dsu/methods-development/eq-5d-5l. Accessed 2 December 2024.
32. Hernández-Alava M PSaWA. Estimating the relationship between EQ-5D-5L and EQ-5D-3L: results from an English population study. Policy Research Unit in Economic Evaluation of Health and Care Interventions. . Published 30 September 2020; Available from: https://drive.google.com/file/d/1rkOWJqaX6NFCp0brYu1hWo-fndOmOXVx/view. Accessed 10 December 2024.
33. National Institute for Health and Care Excellence. Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy. Technology appraisal guidance [TA687]. Published 31 March 2021; Available from: https://www.nice.org.uk/guidance/ta687. Accessed 20 December 2024.
34. Rugo HS, O'Shaughnessy J, Boyle F, Toi M, Broom R, Blancas I*, et al.* Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: safety and patient-reported outcomes from the monarchE study. Ann Oncol. 2022; 33:616-27.
35. National Institute for Health and Care Excellence. Ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer. Technology appraisal guidance [TA496]. Published 20 December 2017; Available from: https://www.nice.org.uk/guidance/ta496. Accessed 20 December 2024.
36. National Institute for Health and Care Excellence. Advanced breast cancer: diagnosis and treatment. Clinical guideline [CG81]. Published 23 February 2009; Available from: https://www.nice.org.uk/guidance/cg81. Accessed 2 December 2024.
37. National Health Service. NHS Reference Costs 2022/2023. Published 27 November 2024; Available from: https://app.powerbi.com/view?r=eyJrIjoiOTQwZjIwMjUtNDgwMi00MThmLWJhM2MtNmM5YWY2MTkwM2M4IiwidCI6IjM3YzM1NGIyLTg1YjAtNDdmNS1iMjIyLTA3YjQ4ZDc3NGVlMyJ9. Accessed 20 December 2024.
38. National Institute for Health and Care Excellence. Neratinib for extended adjuvant treatment of hormone receptor-positive, HER2-positive early stage breast cancer after adjuvant trastuzumab. Technology appraisal guidance [TA612]. Published 20 November 2019; Available from: https://www.nice.org.uk/guidance/ta612. Accessed 2 December 2024.
39. Martín M, Carrasco E, Rodríguez-Lescure Á, Andrés R, Servitja S, Antón A*, et al.* Long-term outcomes of high-risk HR-positive and HER2-negative early breast cancer patients from GEICAM adjuvant studies and El Álamo IV registry. Breast Cancer Res Treat. 2023; 201:151-9.
40. Cuzick J, Sestak I, Baum M, Buzdar A, Howell A, Dowsett M*, et al.* Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. The Lancet Oncology. 2010; 11:1135-41.
41. National Health Service. NHS Reference Costs 2023/2024 Published 29 November 2024; Available from: https://app.powerbi.com/view?r=eyJrIjoiZGQxYjNkOGUtOTIwMC00N2VjLWEyM2EtYjAzOGMwNWU5ODQ1IiwidCI6IjM3YzM1NGIyLTg1YjAtNDdmNS1iMjIyLTA3YjQ4ZDc3NGVlMyJ9. Accessed 20 December 2024.
42. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012; 12:9.

43. Jiang T, Youn B, Paradis AD, Beckerman R, Barnieh L, Johnson NB. A critical appraisal of matching-adjusted indirect comparisons in spinal muscular atrophy. Adv Ther. 2023; 40:2985-3005.

8 APPENDICES

8.1 Appendix 1: EAG summary and critique of the company statistical approaches to MAICs and reweighted IPD analysis

Table 49 EAG summary and critique of the company statistical approaches to MAICs and reweighted IPD analysis

Item	EAG assessment	Summary of company approach	EAG comments
Were ITCs informed by relevant comparators?	Yes	The company conducted relevant population-adjusted MAICs and reweighted IPD analysis to compare the relative efficacy of ribociclib+AI vs abemaciclib+ET and vs ET (adjusted for potential confounding effects due to observed differences in baseline prognostic factors and effect modifiers) using IPD from the NATALEE trial (ribociclib+AI: n=[redacted]; AI: n=[redacted]) and aggregate-level data from Cohort 1 of the monarchE trial[12] (abemaciclib+ET: n=2555). Population 4 median follow-up was [redacted] months (April 2024 DCO). MonarchE trial[12] median follow-up was 54.0 months (July 2023 DCO); these data were used to inform the company's MAICs and reweighted IPD analysis.	The EAG agrees that, in the absence of head-to-head trial data, ITC methods are required to provide relative treatment effect estimates for the comparison of ribociclib+AI vs abemaciclib+ET and vs ET.
Were adjusted ITCs conducted for all relevant outcomes?	Yes	The company performed MAICs for iDFS, OS and safety outcomes of Grade ≥3 TEAEs (with incidence ≥5%), namely increased ALT, diarrhoea, leukopenia, lymphopenia and neutropenia (CS; Section B.2.8.5). The company also performed STC analyses for iDFS, OS and DRFS.	The company iDFS and OS MAICs were informed by monarchE trial[12] Cohort 1 data; however, MAICs for Grade ≥3 TEAEs appear to be based on monarchE trial[22] safety population data, i.e., monarchE trial[22] Cohort 1 and Cohort 2 data; abemaciclib+ET is not an NHS treatment option for patients in Cohort 2 (TA810[9]). This raises concerns about the generalisability of safety MAIC results to NHS patients. The company did not conduct MAICs for tolerability outcomes (e.g., discontinuation rates or PROs). The EAG considers that it may not have been possible to conduct meaningful MAIC analyses of tolerability and HRQoL outcomes due to possible low event rates in the NATALEE trial and in the monarchE trial[22] and differences in HRQoL assessment methods.
Were populations comparable?	Yes	The company performed a population selection step to align study populations prior to conducting the MAICs and reweighted IPD analysis; patients in the NATALEE trial were selected as per the population included in the monarchE trial.[12] The company suggested that the NATALEE trial included a broader population than the monarchE trial[12] and therefore the company considered	In principle, the EAG agrees that this initial 'equalisation' of trial populations is an appropriate step to carry out prior to conducting MAICs and reweighted IPD analyses. This step was carried out to improve comparability between trials prior to population adjustment and involved selecting the NATALEE trial patients who met the monarchE trial[12] eligibility criteria. Data from these patients were

Item	EAG assessment	Summary of company approach	EAG comments
		that it was feasible to evaluate only patients enrolled in the NATALEE trial who had the high-risk of recurrence and nodal status characteristics required for eligibility in the monarchE trial, i.e., Population 4 (the 'NATALEE-selected' population).	subsequently used in the analyses. This selection process is discussed further in Appendix 2, Section 8.2.1. The EAG, however, has concerns that this step breaks NATALEE trial randomisation, which is important as comparative efficacy has been estimated using data from both arms of the NATALEE trial (i.e., ribociclib+AI and AI arms). Furthermore, the NATALEE trial was not powered to detect differences between ribociclib+AI vs AI in this subpopulation. Nevertheless, the EAG considers that this equalisation step is anticipated to reduce between-study heterogeneity when matching the NATALEE trial to the monarchE trial.
Adjustment for covariates	Partly	The company performed unanchored MAICs for two efficacy outcomes (iDFS and OS) using IPD from the NATALEE trial (denoted the index study) through implementation of reweighting using a method-of-moments approach to overcome observed imbalances in trial populations. Nineteen factors across the following 18 unique baseline patient demographic and disease characteristics were included in the primary MAIC: age, sex, race, ethnicity, weight, BMI, geographical region, pathological diagnosis term, hormone receptor status, menopausal status, positive ALNs, histopathology at diagnosis, Ki-67 index, ECOG PS, TNM stage, tumour side, tumour size, prior chemotherapies and prior radiotherapy. A summary of baseline characteristics prior to and after weighting NATALEE trial data is presented in the CS (Table 32, pp96-100). In a sensitivity analysis conducted by the company (CS, Appendix D.7.2 and D.9.2), 4/19 factors (sex, race, ethnicity and region) were omitted from the matching process; the selection of factors retained in the sensitivity analysis was based an assessment of prognostic value according to clinicians as interaction tests and/or tests of prognostic factors. The MAIC sensitivity analysis results were consistent with the primary MAIC results.	Clinical advice to the EAG is that potentially important prognostic factors and treatment effect modifiers were included in the matching process. The EAG agrees with the company (CS, p95 and CS, Table 32) that, after weighting, NATALEE trial and monarchE trial[12] baseline characteristics were suitably balanced across the factors included in the matching process. To overcome observed differences in trial populations, the company weighted a broad set of patient demographic and disease characteristics. Given the strong assumptions underpinning unanchored MAICs, the EAG supports the company's approach of incorporating a large set of baseline factors into the matching process. Unanchored MAICs effectively assume that absolute outcomes can be predicted from the covariates (i.e., that all effect modifiers and prognostic factors have been accounted for in the matching). However, the large number of factors included in the weighting raises concerns that multicollinearity is likely to have been introduced, which occurs when two or more factors are highly correlated (i.e., there is a strong relationship between two or more predictors such that some predictors do not provide any unique information in the matching). In addition, based on the number of levels per factor included in the matching, the EAG has concerns that data may be split sparsely across factors. This may mean that there were few observations across combinations of strata of factors, and this may cause parameter estimation problems. These concerns are also considered to extend to the sensitivity analysis; despite exclusion of four factors, the matching process is still informed by a large number of patient characteristics. The extent to which multicollinearity is present in the company's MAICs is

Item	EAG assessment	Summary of company approach	EAG comments
			unclear. The company did not perform a sensitivity analysis following a correlation assessment, i.e., retaining a broad but parsimonious set of patient demographic and disease characteristics. This approach would have allowed uncertainty around comparative efficacy results to have been explored and would have assessed the impact of multicollinearity on the ESS. The EAG recognises that the MAIC is a trade-off between matching all important prognostic factors and effect modifiers (in order to mitigate the issue of residual confounding) and retaining as much information as possible whilst avoiding substantial reductions in the ESS
Were adjusted ITC methods appropriate?	Yes	The methods used in the company's MAICs are described in the CS (Section B.2.8, Appendix D.7 and Appendix D.9) and the company's response to clarification questions A9 and A10. The company stated that reconstructed IPD for iDFS and OS from published monarchE K-M curves were generated using an adaptation of a published algorithm by Guyot 2012[42] and the company confirmed that recreated K-M curves were visually examined to verify their accuracy compared to the respective published curves. The company then utilised these recreated data to inform the indirect comparison. In response to clarification question A9, the company presented iDFS, OS and DRFS results generated by an STC analysis as an alternative approach to the MAIC. The company performed an STC through use of a predictive equation, modelling the relationship between outcomes and identified prognostic factors and effect modifiers and the calculation of an adjustment factor which was then applied to iDFS TTE data. Following this adjustment, a Cox regression model was fitted to derive a HR and associated 95% CI. In response to clarification question A10, the company also presented iDFS results generated using a time-varying HR approach that involved including an interaction term between time and treatment arm in a Cox regression model; the company concluded that the HR did not vary by time (based on the lack of statistical significance of this term in the model).	The EAG considers that MAIC methods have been correctly implemented by the company; however, the EAG has concerns about the robustness of the analyses. For example, in the company MAICs, NATALEE trial ribociclib+AI and AI arms were reduced in size by [redacted]% and [redacted]%, respectively. The company stated that "comparison of baseline characteristics demonstrated that the trials were well-balanced for many of the reported characteristics at baseline" (CS, Section B.2.8.2, p87); however, the reductions in ESS were substantial. Similarly, for the company sensitivity analyses, despite the company's adjustment for a reduced set of factors, there remained a large reduction in ESS, with NATALEE trial ribociclib+AI and AI arms reduced in size by [redacted]% and [redacted]%, respectively. These reductions in ESS may be due to the inclusion of a large number of factors (it is unclear whether all these factors contribute unique information to the matching); when the ESS is markedly reduced, this may lead to imprecise or unreliable MAIC results. The company's iDFS, OS and DRFS STCs also included adjustments for a large number of prognostic factors and effect modifiers and was based on a regression adjustment approach. The EAG considers that the STC presented in the company response to clarification question A9 has been accurately implemented.
Was the PH assumption	Partly	As Cox PH models were used to estimate HRs and 95% CIs, the company assessed the validity of the iDFS and OS PH assumption	The EAG agrees with the company that it is important to validate the PH assumption. The company stated that the PH assumption

Item	EAG assessment	Summary of company approach	EAG comments
appropriately assessed within the adjusted ITCs of iDFS and OS?		for the comparison of ribociclib+AI vs abemaciclib+ET. The company evaluated the iDFS and OS PH assumptions using a global Schoenfeld residuals test of PH in the MAICs and MAIC sensitivity analyses (CS, Appendix D.9.1 and D.9.2). In response to clarification question A10, the company submitted a corrected PH assessment. The findings from the company's PH test based on weighted iDFS and OS for ribociclib+AI vs abemaciclib+ET yielded statistically non-significant p-values (p=[redacted] and p=[redacted], respectively). Based on this assessment, the company concluded that there was no evidence of violation of the PH assumption. In response to clarification question A10, the company performed a time-varying MAIC as an alternative to using a constant HR approach for iDFS which showed a statistically non-significant interaction term between time and treatment arm.	was tested based on visual inspection of the log-cumulative hazard plots (not presented by the company), Schoenfeld residual plots (company response to clarification question A10, Figure 16 and Figure 17) and the global test of PH. The Cox PH model is only an appropriate method if the PH assumption holds; based on the company's updated and corrected assessment of the PH assumption, the EAG considers that the use of constant HRs for ribociclib+AI vs abemaciclib+ET may provide an appropriate measure of comparative efficacy for iDFS and OS.
Was the presentation of adjusted ITC results appropriate?	Yes	For the iDFS and OS MAICs for the comparison of ribociclib+AI vs abemaciclib+ET and for the reweighted IPD analysis for the comparison of ribociclib+AI vs ET, the company presented (CS, Section 2.8.5) K-M curves and constant HR results (with 95% CIs), both prior to and after weighting. The company also presented ORs (with 95% CIs) to estimate comparative safety between ribociclib+AI vs abemaciclib+ET for five Grade ≥3 TEAEs. In response to clarification question A9, the company also presented constant HR STC results.	The EAG considers the presentation of MAIC, STC and reweighted IPD analysis results was appropriate.

AI=aromatase inhibitor; ALN=axillary lymph node; ALT=alanine transaminase; BMI=body mass index; CI=confidence interval; CS=company submission; DDFS=distant disease-free survival; EAG=External Assessment Group; ECOG PS=Eastern Cooperative Oncology Group performance status; ESS=effective sample size; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; HR=hazard ratio; HRQoL=health-related quality of life; iDFS=invasive disease-free survival; IPD=individual patient data; ITC=indirect treatment comparison; Ki67=Kiel 67; K-M=Kaplan-Meier; MAIC=matching-adjusted indirect comparison; NHS=National Health Service; NICE=National Institute for Health and Care Excellence; OR=odds ratio; OS=overall survival; PH=proportional hazards; PRO=patient reported outcomes; RFS=recurrence-free survival; STC=simulated treatment comparison; TEAE=treatment-emergent adverse event; TNM=tumour-node-metastasis
Source: CS, Section B.2.8, Appendix D; company response to clarification questions A9 and A10

8.2 Appendix 2: Indirect treatment comparisons

8.2.1 Equalisation of trial populations

Prior to conducting the MAICs and reweighted IPD analysis, the company performed an initial 'equalisation' step to align the trial populations; the company suggested that the NATALEE trial evaluates a broader population than the monarchE trial and therefore the company considered it feasible to evaluate only patients enrolled in the NATALEE trial who were eligible to enrol in the monarchE trial, i.e., patients with high risk of recurrence and nodal status characteristics required for eligibility in the monarchE trial, referred to by the company as the 'NATALEE-selected' population (i.e., Population 4). The company's MAIC for TTE outcomes included patients receiving ribociclib+AI (n=[redacted]) and AI (n=[redacted]) from the NATALEE trial Population 4 as well as patients receiving abemaciclib+ET (n=2555) from the monarchE trial Cohort 1.

The EAG agrees with the company's approach to apply the inclusion/exclusion criteria of the monarchE trial to the NATALEE trial (i.e., where IPD are available) so that only patients from the NATALEE trial who meet the eligibility criteria of the monarchE trial are retained for inclusion in the MAICs and reweighted IPD analysis, to increase comparability of trials prior to population-adjustment.[43] The EAG does, however, have concerns that this equalisation step breaks trial randomisation in the NATALEE trial, particularly in the company reweighted IPD analysis as comparative efficacy for ribociclib+AI versus ET has been estimated using both arms of the NATALEE trial (NATALEE trial AI data were used to inform the efficacy of ET in the comparison of ribociclib+AI versus ET). Furthermore, eligibility for treatment with abemaciclib+ET was not a pre-specified subgroup analysis and therefore the trial was not powered to detect differences between ribociclib+AI versus ET for Population 4 (i.e., patients eligible for treatment with abemaciclib+ET). However, the EAG believes that the approach to 'equalise' study populations as far as possible, prior to population-adjustment outweighs these limitations and may help to reduce between-study heterogeneity.

8.2.2 Patient baseline characteristics

In response to clarification question A8, the company confirmed that, in regard to missing values in the monarchE trial, matching was performed to 'missing' categories where there were also missing patients in the NATALEE trial for a specific baseline characteristic. In instances where no patients were missing in the NATALEE trial for a given baseline characteristic, patients with 'missing' values in the monarchE trial were excluded and the proportions across non-missing categories were recalibrated accordingly; the EAG considers this to be a reasonable approach.

Table 50 Patient baseline characteristics in Cohort 1 of the monarchE trial and NATALEE-selected trial prior to and after weighting

Characteristic	monarchE[12] (Cohort 1)		NATALEE-selected, unweighted (Population 4)		NATALEE-selected, weighted (Population 4b)	
	Abemaciclib+ET (N=2555)	ET (N=2565)	Ribociclib+AI (N=[redacted])	AI[a] (N=[redacted])	Ribociclib+AI (ESS=[redacted])	AI[a] (ESS=[redacted])
Age, years						
Mean	52.2	52.2	[redacted]	[redacted]	[redacted]	[redacted]
<65, %	84.1%	85.4%	[redacted]	[redacted]	[redacted]	[redacted]
≥65, %	15.9%	14.6%	[redacted]	[redacted]	[redacted]	[redacted]
Female, %	99.2%	99.2%	[redacted]	[redacted]	[redacted]	[redacted]
Race, %						
Asian	24.7%	23.9%	[redacted]	[redacted]	[redacted]	[redacted]
White	70.6%	71.0%	[redacted]	[redacted]	[redacted]	[redacted]
Other	4.7%	5.1%	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity, %						
Hispanic or Latino	8.0%	8.9%	[redacted]	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	92.0%	91.1%	[redacted]	[redacted]	[redacted]	[redacted]
Missing	0.0%	0.0%	[redacted]	[redacted]	[redacted]	[redacted]
Region, %						
North America/Europe	51.8%	51.9%	[redacted]	[redacted]	[redacted]	[redacted]
Asia	20.4%	20.4%	[redacted]	[redacted]	[redacted]	[redacted]
Other	27.8%	27.7%	[redacted]	[redacted]	[redacted]	[redacted]
Weight, kg, mean	71.3	71.7	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m2, mean	27.2	27.4	[redacted]	[redacted]	[redacted]	[redacted]
Pathological diagnosis term, %						
Invasive ductal breast carcinoma	67.3%	68.7%	[redacted]	[redacted]	[redacted]	[redacted]
Invasive lobular breast carcinoma	13.9%	13.1%	[redacted]	[redacted]	[redacted]	[redacted]
Tubular breast carcinoma	0.1%	0.2%	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	monarchE[12] (Cohort 1)		NATALEE-selected, unweighted (Population 4)		NATALEE-selected, weighted (Population 4b)	
	Abemaciclib+ET (N=2555)	ET (N=2565)	Ribociclib+AI (N=[redacted])	AI[a] (N=[redacted])	Ribociclib+AI (ESS=[redacted])	AI[a] (ESS=[redacted])
Other	18.7%	18.1%	[redacted]	[redacted]	[redacted]	[redacted]
HR status, %						
ER-positive	99.3%	99.3%	[redacted]	[redacted]	[redacted]	[redacted]
ER-negative	0.5%	0.6%	[redacted]	[redacted]	[redacted]	[redacted]
ER missing	0.2%	0.0%	[redacted]	[redacted]	[redacted]	[redacted]
PR-positive	86.4%	86.8%	[redacted]	[redacted]	[redacted]	[redacted]
PR-negative	10.5%	10.5%	[redacted]	[redacted]	[redacted]	[redacted]
PR missing	3.1%	2.7%	[redacted]	[redacted]	[redacted]	[redacted]
Menopausal status, %						
Pre-menopausal	43.7%	43.1%	[redacted]	[redacted]	[redacted]	[redacted]
Post-menopausal	56.3%	56.9%	[redacted]	[redacted]	[redacted]	[redacted]
Positive axillary lymph nodes, %						
0	0.2%	0.2%	[redacted]	[redacted]	[redacted]	[redacted]
1 to 3	34.2%	34.6%	[redacted]	[redacted]	[redacted]	[redacted]
≥4	65.6%	65.1%	[redacted]	[redacted]	[redacted]	[redacted]
Histopathology at diagnosis, %						
Grade 1	7.3%	7.4%	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2	46.2%	46.5%	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3	41.6%	40.9%	[redacted]	[redacted]	[redacted]	[redacted]
Not assessed/missing	4.9%	5.1%	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS						
0	85.4%	83.7%	[redacted]	[redacted]	[redacted]	[redacted]
1	14.5%	16.1%	[redacted]	[redacted]	[redacted]	[redacted]
2, 3 and missing	0.1%	0.2%	[redacted]	[redacted]	[redacted]	[redacted]
Tumour side						

Characteristic	monarchE[12] (Cohort 1)		NATALEE-selected, unweighted (Population 4)		NATALEE-selected, weighted (Population 4b)	
	Abemaciclib+ET (N=2555)	ET (N=2565)	Ribociclib+AI (N=[redacted])	AI[a] (N=[redacted])	Ribociclib+AI (ESS=[redacted])	AI[a] (ESS=[redacted])
Left	51.8%	49.8%	[redacted]	[redacted]	[redacted]	[redacted]
Right	46.6%	49.1%	[redacted]	[redacted]	[redacted]	[redacted]
Bilateral	1.6%	1.1%	[redacted]	[redacted]	[redacted]	[redacted]
Pathologic tumour size (cm), %						
<2	26.5%	25.6%	[redacted]	[redacted]	[redacted]	[redacted]
2 to 5	48.3%	49.8%	[redacted]	[redacted]	[redacted]	[redacted]
≥5	23.5%	23.6%	[redacted]	[redacted]	[redacted]	[redacted]
Missing	1.8%	1.0%	[redacted]	[redacted]	[redacted]	[redacted]
Ki-67 Index, %						
<20	37.0%	37.7%	[redacted]	[redacted]	[redacted]	[redacted]
≥20	39.8%	38.4%	[redacted]	[redacted]	[redacted]	[redacted]
Missing	23.2%	23.9%	[redacted]	[redacted]	[redacted]	[redacted]
TNM stage, %						
IA	0.0%	0.0%	[redacted]	[redacted]	[redacted]	[redacted]
IB	0.0%	0.0%	[redacted]	[redacted]	[redacted]	[redacted]
IIA	9.0%	9.7%	[redacted]	[redacted]	[redacted]	[redacted]
IIB	11.0%	11.2%	[redacted]	[redacted]	[redacted]	[redacted]
IIIA	40.0%	39.7%	[redacted]	[redacted]	[redacted]	[redacted]
IIIB	3.8%	3.3%	[redacted]	[redacted]	[redacted]	[redacted]
IIIC	35.8%	36.1%	[redacted]	[redacted]	[redacted]	[redacted]
Missing	0.4%	0.2%	[redacted]	[redacted]	[redacted]	[redacted]
Prior chemotherapy, %						
Neoadjuvant	36.5%	36.3%	[redacted]	[redacted]	[redacted]	[redacted]
Adjuvant	58.7%	58.6%	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	monarchE[12] (Cohort 1)		NATALEE-selected, unweighted (Population 4)		NATALEE-selected, weighted (Population 4b)	
	Abemaciclib+ET (N=2555)	ET (N=2565)	Ribociclib+AI (N=[redacted])	AI[a] (N=[redacted])	Ribociclib+AI (ESS=[redacted])	AI[a] (ESS=[redacted])
None	4.8%	5.1%	[redacted]	[redacted]	[redacted]	[redacted]
Prior radiotherapy, %	96.0%	96.1%	[redacted]	[redacted]	[redacted]	[redacted]

[a] NATALEE trial AI data were used to inform the efficacy of ET in the comparison of ribociclib+AI versus ET
AI=aromatase inhibitor; BMI=body mass index; CDK4/6=cyclin-dependent kinases 4/6; ECOG PS=Eastern Cooperative Oncology Group performance status; ER=oestrogen receptor; Ki-67=antigen Kiel-67; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; TNM=tumour-node-metastasis
Source: CS, Table 32

8.3 Appendix 3: EAG revisions to the company model

This appendix contains details of the changes that the EAG made to the company model.

<table>
<tr><th>EAG revisions</th><th>Implementation instructions</th></tr>
<tr><td>Set up: EAG revision switches</td><td>In sheet ‘Results’

Paste the following table into cells M11:O19
<table>
<tr><th>Name</th><th>Switch</th><th>Description</th></tr>
<tr><td>EAGScen1</td><td>0</td><td>Set ET iDFS event distribution to equal ribociclib</td></tr>
<tr><td>EAGScen2</td><td>0</td><td>Change ribociclib PFS and OS in DR state</td></tr>
<tr><td>EAGScen3</td><td>0</td><td>Change % CDK4/6 sensitive patients receiving subsequent CDK4/6 in ET resistant state</td></tr>
<tr><td>EAGScen4</td><td>0</td><td>Change % ribociclib & abe patients receiving subsequent CDK4/6 in ET sensitive state</td></tr>
<tr><td>EAGScen5</td><td>0</td><td>Change ET-sensitive PF utility to equal NMR utility</td></tr>
<tr><td>EAGScen6</td><td>0</td><td>Change AE unit costs</td></tr>
<tr><td>EAGScen7</td><td>0</td><td>Treatment effect waning length</td></tr>
<tr><td>FACupdate1</td><td>0</td><td>Cells I11:I16 on the ‘Efficacy Waning’ tab in the CEM for all populations.</td></tr>
<tr><td>FACupdate2</td><td>0</td><td>Cells Y16:Y12 on the ‘Comp2.Calc’ tab in the CEM for all populations.</td></tr>
</table>
Use names in ‘Name’ column to name the cells in the ‘Switch’ column</td></tr>
<tr><td>Set up: define new scenarios:
• ‘EAG FAC base case_Population 1’
• ‘EAG FAC base case_Population 4B’</td><td>For each EAG FAC scenario:

1. Load appropriate company scenario:
a. load ‘Population 1 (NATALEE ITT)’ for ‘EAG FAC base case_Population 1’
b. load ‘Population 4B (weighted node-positive high-risk eligible for abemaciclib)’ for ‘EAG FAC base case_Population 4B’
2. For the first scenario, make all the revisions in the table below
3. Save the first scenario
4. Load the second company scenario
5. Repeat all the revisions in the table below
6. Save the second scenario</td></tr>
</table>

Errors: make company FAC updates to company base case	In sheet 'Efficacy Waning' Set formula in cell I11 = IF(FACupdate1=0,Comp1.Calc!$F$219,Comp1.Calc!$F$219*model.months.cycle) Set formula in cell I12 = IF(FACupdate1=0,Comp2.Calc!$F$219,Comp2.Calc!$F$219*model.months.cycle) Set formula in cell I13 = IF(FACupdate1=0,Comp3.Calc!$F$219,Comp3.Calc!$F$219*model.months.cycle) In sheet 'Comp2.Calc' Set formula in cell Y6 = IF(FACupdate2=0,IF(OR(W6="",W6="Goserelin"),"",X6),IF(OR(W6="",W6="Goserelin", W6="Zoledronic acid"),"",X6)) Copy cell formula down from Y6:Y12
R1) Set ET iDFS event distribution to equal ribociclib	In sheet 'Efficacy IDFS' Set value in cells I13 = IF(EAGScen1=0,0.0324483775811209,comp1.idfs_death_1) Set value in cells J13 = IF(EAGScen1=0,0.654867256637168, comp1.idfs_dr_1) Set value in cells K13 = IF(EAGScen1=0,0.117994100294985,comp1.idfs_spm_1)
R2) Choose alternative ribociclib+AI PFS and OS in DR state	**Use existing model functionality** **NOTE: these cells reset on loading a model population** In sheet 'Efficacy ET resist' Set cell E17 = "OS: ML3 R+F Weibull (R)" Set cell E18 = "PFS: ML3 R+F Exponential" Set cell E20 = "PFS: ML3 R+F Exponential" In sheet 'Efficacy ET sensitive' Set cell E17 = "OS: ML2 R+LZE Gamma" Set cell E18 = "PFS: ML2 R+LZE Exponential" Set cell E20 = "PFS: ML2 R+LZE Exponential"

R3) Change % ET resistant state CDK4/6 sensitive patients receiving subsequent CDK4/6	In sheet 'Results' Paste the following values into cells T24:U31 0 | 0.6 0.3 | 0.3 0.6 | 0 0.007 | 0.007 0.0385 | 0.0385 0.0175 | 0.0175 0.007 | 0.007 Assign name to range T22:T28 = EAG_ETres_CDKsens_TxMix_ribo Assign name to range U22:U28 = EAG_ETres_CDKsens_TxMix_abe In sheet 'Treatment Mix ET Resist' Paste the following table into cells E27:E33 = IF(EAGScen3=0,0, INDEX(EAG_ETres_CDKsens_TxMix_ribo,1)) = IF(EAGScen3=0,0.1, INDEX(EAG_ETres_CDKsens_TxMix_ribo,2)) = IF(EAGScen3=0,0.2, INDEX(EAG_ETres_CDKsens_TxMix_ribo,3)) = IF(EAGScen3=0,0.07, INDEX(EAG_ETres_CDKsens_TxMix_ribo,4)) = IF(EAGScen3=0,0.385, INDEX(EAG_ETres_CDKsens_TxMix_ribo,5)) = IF(EAGScen3=0,0.175, INDEX(EAG_ETres_CDKsens_TxMix_ribo,6)) = IF(EAGScen3=0,0.07, INDEX(EAG_ETres_CDKsens_TxMix_ribo,7)) Paste the following table into cells G27:G33 = IF(EAGScen3=0,0.2, INDEX(EAG_ETres_CDKsens_TxMix_abe,1)) = IF(EAGScen3=0,0.1, INDEX(EAG_ETres_CDKsens_TxMix_abe,2)) = IF(EAGScen3=0,0, INDEX(EAG_ETres_CDKsens_TxMix_abe,3)) = IF(EAGScen3=0,0.07, INDEX(EAG_ETres_CDKsens_TxMix_abe,4)) = IF(EAGScen3=0,0.385, INDEX(EAG_ETres_CDKsens_TxMix_abe,5)) = IF(EAGScen3=0,0.175, INDEX(EAG_ETres_CDKsens_TxMix_abe,6)) = IF(EAGScen3=0,0.07, INDEX(EAG_ETres_CDKsens_TxMix_abe,7))

<table>
<tr>
<td>R4) Change % ET sensitive state CDK4/6 sensitive patients receiving subsequent CDK4/6</td>
<td>
<u>In sheet ‘Results’</u>

Paste the following values into cells V24:V28

<table>
<tr><td>0.4</td></tr>
<tr><td>0.1</td></tr>
<tr><td>0.4</td></tr>
<tr><td>0.1</td></tr>
</table>

Assign name to range V22:V25 = EAG_ETsens_TxMix

<u>In sheet ‘Treatment Mix ET Sensitive’</u>

Paste the following table into cells E12:E15 and cells G12:G15

<table>
<tr><td>=IF(EAGScen4=0,0.2 ,INDEX(EAG_ETsens_TxMix,1))</td></tr>
<tr><td>=IF(EAGScen4=0,0.05, INDEX(EAG_ETsens_TxMix,2))</td></tr>
<tr><td>=IF(EAGScen4=0,0.2, INDEX(EAG_ETsens_TxMix,3))</td></tr>
<tr><td>=IF(EAGScen4=0,0.55, INDEX(EAG_ETsens_TxMix,4))</td></tr>
</table>
</td>
</tr>
<tr>
<td>R5) Change ET-sensitive PF utility to equal NMR utility</td>
<td>
<u>In sheet ‘Utilities State’</u>

Set value in cell G30 =
IF(EAGScen5=0, 0.618884654568206, comp1.util_nmr)

Set value in cells G31 =
IF(EAGScen5=0, 0.618884654568206, comp2.util_nmr)

Set value in cells G32 =
IF(EAGScen5=0, 0.618979268918502, comp3.util_nmr)
</td>
</tr>
</table>

<table>
<tr>
<td>R6) Change AE unit costs</td>
<td>
<u>In sheet ‘Results’</u>

Paste the following values into cells W24:W29

<table>
<tr><td>792</td></tr>
<tr><td>1975</td></tr>
<tr><td>1454</td></tr>
<tr><td>1454</td></tr>
<tr><td>2174</td></tr>
</table>

Assign name to range W22:W26 = EAG_AE_costs

<u>In sheet ‘AE Incidence’</u>

Paste the following table into cells K11:K15

<table>
<tr><td>=IF(EAGScen6=0, 190.526392276169, INDEX(EAG_AE_costs,1))</td></tr>
<tr><td>=IF(EAGScen6=0, 190.526392276169, INDEX(EAG_AE_costs,2))</td></tr>
<tr><td>=IF(EAGScen6=0, 190.526392276169, INDEX(EAG_AE_costs,3))</td></tr>
<tr><td>=IF(EAGScen6=0, 190.526392276169, INDEX(EAG_AE_costs,4))</td></tr>
<tr><td>=IF(EAGScen6=0, 190.526392276169, INDEX(EAG_AE_costs,5))</td></tr>
</table>
</td>
</tr>
</table>

S1 and S2 Treatment effect waning length	In sheet 'Results Assign name to cell S18 = EAGTxWaneStart Assign name to cell U18 = EAGTxWaneEnd For S1 Treatment effect waning for ribociclib+AI (and abemaciclib+ET): 5 to 8 years Set EAGTxWaneStart = 5 Set EAGTxWaneEnd = 8 For S2 Remove treatment waning Set EAGTxWaneStart = 60 Set EAGTxWaneEnd = 0 In sheet 'Efficacy Waning' Set value in cell G11 = IF(EAGScen7=0,8*12,EAGTxWaneStart*12) Set value in cell H11 = IFS(EAGScen7=0,('Efficacy Waning'!$I$11-comp1.wane_idfs_start), AND(EAGScen7=1,EAGTxWaneEnd<=EAGTxWaneStart),('Efficacy Waning'!$I$11-comp1.wane_idfs_start), AND(EAGScen7=1,EAGTxWaneEnd>EAGTxWaneStart),EAGTxWaneEnd*12-comp1.wane_idfs_start)

Additional PSA adjustments	**NOTE: This sets the PSA for the complete EAG scenario for each population. To remove the full PSA setting for a given revision after setting the Switch on the Results sheet to 0, set the relevant distribution in column G to the base case value** In sheet 'PA Inputs' PSA for R1) Paste the following table into cells F155:F158 =IF(EAGScen1=0,"","_psa_comp1.idfs_death_1") =IF(EAGScen1=0,"","_psa_comp1.idfs_dr_1") =IF(EAGScen1=0,"","_psa_comp1.idfs_spm_1") =IF(EAGScen1=0,"","_psa_comp1.idfs_nmr_1") Set value in cells G155:G158 to 'Link' **[[remove by setting to 'Empirical Distribution']]** Set value in cell F174 = IF(EAGScen1=0,"","_psa_comp1.idfs_nmr_1") Set value in cells G174 to 'Link' **[[remove by setting to 'Empirical Distribution']]** ------ PSA for R3) Paste the following table into cells L2105:L2111 = IF(EAGScen3=0,0, INDEX(EAG_ETres_CDKsens_TxMix_ribo,1)*100) = IF(EAGScen3=0,10, INDEX(EAG_ETres_CDKsens_TxMix_ribo,2)*100) = IF(EAGScen3=0,20, INDEX(EAG_ETres_CDKsens_TxMix_ribo,3)*100) = IF(EAGScen3=0,7, INDEX(EAG_ETres_CDKsens_TxMix_ribo,4)*100) = IF(EAGScen3=0,38.5, INDEX(EAG_ETres_CDKsens_TxMix_ribo,5)*100) = IF(EAGScen3=0,17.5, INDEX(EAG_ETres_CDKsens_TxMix_ribo,6)*100) = IF(EAGScen3=0,7, INDEX(EAG_ETres_CDKsens_TxMix_ribo,7)*100) Paste the following table into cells L2127:L2133 = IF(EAGScen3=0,20, INDEX(EAG_ETres_CDKsens_TxMix_abe,1)*100) = IF(EAGScen3=0,10, INDEX(EAG_ETres_CDKsens_TxMix_abe,2)*100) = IF(EAGScen3=0,0, INDEX(EAG_ETres_CDKsens_TxMix_abe,3)*100) = IF(EAGScen3=0,7, INDEX(EAG_ETres_CDKsens_TxMix_abe,4)*100) = IF(EAGScen3=0,38.5, INDEX(EAG_ETres_CDKsens_TxMix_abe,5)*100)

	= IF(EAGScen3=0,17.5, INDEX(EAG_ETres_CDKsens_TxMix_abe,6)*100)
	= IF(EAGScen3=0,7, INDEX(EAG_ETres_CDKsens_TxMix_abe,7)*100)

PSA for R4)

Paste the following table into cells L1892:L1895 and cells L1914:L1917

=IF(EAGScen4=0,20,INDEX(EAG_ETsens_TxMix,1)*100)
=IF(EAGScen4=0,5, INDEX(EAG_ETsens_TxMix,2)*100)
=IF(EAGScen4=0,20, INDEX(EAG_ETsens_TxMix,3)*100)
=IF(EAGScen4=0,55, INDEX(EAG_ETsens_TxMix,4)*100)

PSA for R5)

Paste the following table into cells F2049:F2051

=IF(EAGScen5=0,"_psa_comp2.util_et_sens_pfs","_psa_comp1.util_nmr")
=IF(EAGScen5=0,"","_psa_comp2.util_nmr")
=IF(EAGScen5=0,"_psa_comp2.util_et_sens_pfs","_psa_comp3.util_nmr")

Set value in cell G2050 to 'Link' **[[remove by setting to 'Multivariate Normal']]**

NOTE: remember to Save scenario

AE=adverse event; AI=aromatase inhibitor; CDK=cyclin-dependent kinases; DR=distant recurrence; EAG=External Assessment Group; ET=endocrine therapy; iDFS=invasive disease-free survival; NMR=non-metastatic recurrence; OS=overall survival; PF=progression free; PFS=progression-free survival

Single Technology Appraisal

Ribociclib with an aromatase inhibitor for adjuvant treatment of hormone receptor-positive, HER2-negative early breast cancer [ID6153]

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 Tuesday 28 January 2025** 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 [redacted] should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Principal factual inaccuracies

Issue 1 Reference to NATALEE ITT population

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Issue 1, Page 12, Section 1.3 of the EAG report states that *"Focusing on the NATALEE trial ITT population is problematic as the trial comparator is AI; most NHS patients who are eligible for treatment with abemaciclib+ET would be treated with abemaciclib+ET, not ET."* Reference to focusing on the NATALEE ITT population as problematic is misleading, given this population represents the full anticipated licensed population for ribociclib in this indication and the target population for ribociclib in this submission. In addition, the NATALEE ITT population has been validated by clinicians to be a clinically valid population.	Remove reference to the focus on the NATALEE trial ITT population being problematic.	To reduce the potentially misleading nature of the phrasing of Issue 1 and to prevent the magnification of this issue.	This is not a factual inaccuracy. No change required to the EAG report.

Issue 2 Lack of clarity in reporting of clinical input

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Issue 2, Page 12, Section 1.3 and Page 35, Section 3.2.2 of the EAG report references clinical advice to the company regarding adjuvant ET treatment mixes. However, it is unclear where the quoted treatment mixes ([redacted]% of patients receive letrozole, [redacted]% receive anastrozole and the remainder are likely to receive exemestane [redacted] or tamoxifen ([redacted] have been derived from. The estimates presented in the EAG report do not align to the clinical advice provided in the September 2024 clinical validation exercise conducted by the Company where UK clinical experts determined and agreed upon suitable treatment mixes (which then subsequently informed the model). For completeness, the clinically validated estimates for the letrozole, anastrozole, exemestane and tamoxifen treatment mixes in the	Firstly, clarify the derivation of the following ET treatment mixes in the adjuvant setting: ([redacted]% of patients receive letrozole, ([redacted]% receive anastrozole and the remainder are likely to receive exemestane ([redacted] or tamoxifen ([redacted]). Secondly, the Company proposes aligning to the clinically validated adjuvant ET treatment mixes from the September 2024 advisory board.	To provide transparency on the derivation of the ET treatment mixes in the adjuvant setting and to further ensure validated estimates are informing the cost-effectiveness analyses.	The proportions presented in the EAG report (p12 and p35) were based on a combination of clinical advice to the company and clinical advice to the EAG. Text amended as follows and confidential marking applied: Section 1.3, Issue 2 (p12) However, clinical advice to the company is that [redacted] of patients receive letrozole, [redacted] receive anastrozole and the remainder are likely to receive exemestane [redacted] or tamoxifen [redacted] Section 3.2.2, p35 However, clinical advice to the company (CS, Appendix Q.3, Table 110) is that [redacted] of patients receive letrozole, [redacted] receive anastrozole and the remainder are likely to

adjuvant ET setting in Population 1 were: [redacted]%, [redacted]%, [redacted]% and [redacted]%, respectively, for patients receiving ribociclib plus AI, and [redacted]%, [redacted]%, [redacted]% and [redacted]%, respectively, for patients receiving ET alone. Therefore, while acknowledging the potential difference in clinical variation, the source of the EAG's presented treatment mixes, and the rationale for the variation between Company and EAG estimates, is unclear. The Company proposes that the treatment mix estimates for the adjuvant ET setting are updated to align to the clinically validated estimates outlined above.			receive exemestane ([redacted] or tamoxifen [redacted]

Issue 3 Generalisability of the AI arm from NATALEE to clinical practice

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
In Issue 2, Page 12, Section 1.3 of the EAG report, and throughout the EAG report, the	The Company request the EAG include clarification in their report that the approach to use AI data from the	To provide a balanced account and reflect the steps taken by	This is not a factual inaccuracy. No change required to the EAG report.

EAG make multiple references to the AI arm from NATALEE not being appropriate to represent ET. The Company acknowledge that a different treatment mix was used in the AI arm of NATALEE compared to clinical practice, as tamoxifen was not used in the trial but could be used in clinical practice. However, given the evidence presented in Appendix M.1 of the CS demonstrating the reduced efficacy of tamoxifen compared to AIs, the Company consider the EAG should clarify that the use of data from NATALEE is, if anything, a conservative approach. Further, the Company have adjusted the efficacy of the AI arm of NATALEE within the model to account for the poorer efficacy of tamoxifen using a weighted HR approach. This approach aims to address the concerns outlined in this issue and should be highlighted.	NATALEE trial would be conservative and that generalisability concerns have been accounted for in the model.	the Company to mitigate this issue.	

Issue 4 Reference to DDFS preference over IDFS

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Issue 3, Page 13, Section 1.3 of the EAG report states that "*clinical advice to the EAG is that DDFS is a more appropriate proxy for OS than iDFS*" and recommends that clinical opinion is sought on the most relevant proxy for OS. The Company do not consider this to be a key issue to this submission, given iDFS was the primary endpoint of NATALEE trial, and has been confirmed to be an appropriate and meaningful primary outcome for use in prior cost-effectiveness models in this indication (TA810). Additionally, the EAG provide no rationale within the EAG report as to why DDFS is the more appropriate surrogate for OS.	The Company request that the following wording is added to Issue 3: "*However, the use of iDFS, the primary endpoint from the NATALEE trial as a key outcome within the model is still appropriate, and aligns with previously accepted model structures (TA810)*".	To reduce the potentially misleading nature of the phrasing of Issue 3 and to provide a balanced account, thus preventing the magnification of this issue.	This is not a factual inaccuracy. No change required to the EAG report.

Issue 5 Inaccurate description of the model results

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Throughout the EAG report, the EAG state that the cost-effectiveness results may not be robust because OS cannot be directly estimated as a fixed payoff of LYs is assigned for patients in the DR health state. The Company acknowledge the model does not present estimates for the proportion of patients alive across the model time horizon, however, it is not accurate to state that OS cannot directly be estimated. This is because OS is presented in the model in terms of LYs and therefore the current wording may be misinterpreted to mean OS estimates are not available, which is not correct. The model structure uses a fixed LYs payoff in the DR state, which is a methodologically valid approach that was deemed appropriate for decision making	The Company request the EAG change their wording discussing Issue 6, given OS estimates in terms of LYs are calculated within the model.	To accurately report the model structure and outputs.	This is not a factual inaccuracy. However, the EAG has amended the text for clarity. The text has been amended as follows: Section 1.2, p11 The EAG highlights that OS over time (including median OS) cannot be directly estimated from the model due to the payoff approach used to estimate life years in the DR health state and because deaths due to second primary malignancies were not included. Section 1.5, Issue 6, p14 OS over time (including median OS) cannot be directly estimated from the model as a payoff approach was used to calculate life years in the DR health state and deaths due to second primary

in TA810 despite the inability to estimate OS over time. The Company therefore do not consider the model results to lack robustness, but acknowledge the limitations with this model structure mean the underlying OS estimates over time cannot be produced and presented visually.			malignancies were not included. Section 6, p78 The EAG cautions that OS over time (including median OS) cannot be directly estimated from the model due to the approach used to calculate life years in the DR health state. Additionally, patients who transition into the SPM health state exit the model, and so their deaths are not included in the life years calculation and would not be included in any OS estimates. Section 6.1, Table 33 The company model structure is generally appropriate but does not allow OS estimates to be calculated over time (including median OS) so these cannot be validated by the EAG. Additionally, patients who transition into the SPM health state exit the model, and so their

			deaths are not included in the life years calculation. Section 6.7, p95 The EAG considers that until model OS estimates over time (including median OS) can be compared with clinician estimates and published estimates, company and EAG cost effectiveness results may not be robust. The exclusion of deaths from second primary malignancies may prevent model OS outcomes being compared with OS from the literature or prespecified OS measures from the NATALEE trial.

Issue 6 Reporting of Company claims relating to NATALEE trial data

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Issue 7, Page 15, Section 1.5; Page 30, Section 2.4.7; Page 80, Section 6.2 of the EAG report refers to claims by the Company that the efficacy of	Amend the wording on Issue 7, Page 15, Section 1.5; Page 30, Section 2.4.7; and Page 80, Section 6.2 of the EAG report to clarify that the Company did not claim the efficacy of ribociclib+AI versus AI was the	To maintain factual accuracy of the reporting of Company claims relating to efficacy data from NATALEE.	Text amended as follows: Section 1.5, Issue 7, p15 The company stated that "the efficacy of

ribociclib+AI versus AI was the same irrespective of whether patients were eligible or ineligible for treatment with abemaciclib+ET. This is not factually accurate as the Company did not explicitly make this claim. Rather, within the Company's response to clarification question B1, the Company stated that "*baseline characteristics and efficacy data for the NATALEE high-risk ineligible for the abemaciclib population from the NATALEE trial are presented in response to Question A2, which shows the efficacy of ribociclib + AI versus ET in this population is aligned with that of the broader ITT population*." As such, the current wording of the EAG report is misleading and the Company requests that the aforementioned sections of the EAG report are amended to reflect the Company's explicit wording.	same irrespective of whether patients were eligible or ineligible for treatment with abemaciclib+ET. The Company suggests the updated EAG report aligns to the explicit Company wording provided in response to clarification question B1 (i.e., that the "efficacy of ribociclib + AI versus ET in this population is aligned with that of the broader ITT population.").		ribociclib+AI versus ET in [the NATALEE high-risk ineligible for the abemaciclib] population is aligned with that of the broader ITT population". <u>Section 6.2, p81</u> This approach is in line with the company response to clarification question B1 where the company stated that "the efficacy of ribociclib+AI versus ET in [the NATALEE high-risk ineligible for the abemaciclib] population is aligned with that of the broader ITT population".

Issue 7 iDFS event distribution

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Issue 10, Table 10, Page 16, Section 1.5, of the EAG report argues that the same iDFS distributions should be used for all treatments. This is based on the EAG's belief that there is "*insufficient evidence*" to suggest that the distribution of iDFS event types differs between ribociclib+AI and ET, as highlighted throughout the EAG report. Whilst it is accurate to report that the 95% CIs for each treatment overlap, the Company argue it is important to recognise the lack of face validity in the EAG's proposed approach of using the same iDFS distributions for both treatment arms. The efficacy and mechanism of action of ribociclib plus AI inherently leads to improved proportions of iDFS events that are death, SPM, NMR or DR. Notably, clinical validation sought by	The Company proposes amending the wording throughout the EAG report from "*there is insufficient evidence*" to "*the EAG do not believe there is sufficient evidence*" to acknowledge the evidence from the clinical validation exercise presented in Company's response to clarification question B8, and to soften the factual nature of the current phrasing. Secondly, the Company request that the wording of Issue 10 is updated to acknowledge the clinical validity considerations of the EAG's approach.	To reduce the potentially misleading nature of the phrasing of iDFS event distribution evidence and to present a fair account of the EAG's suggest base case change.	Text amended as follows: Section 1.5, Issue 7,p15 For each health state, the 95% CIs for each treatment overlap substantially, indicating that there is insufficient statistical evidence of a difference between the iDFS event distributions based on treatment. Section 6.1, Table 33 There is insufficient statistical evidence to suggest that the distribution of iDFS event types differs between ribociclib+AI and ET. The EAG has adjusted the iDFS event distribution for treatment with ET so that it matches the distribution for ribociclib+AI. Section 6.3.2, p83 In each health state, the 95% CIs for each treatment

the Company validated that a difference in iDFS event types between treatment arms is clinically plausible. Specifically, as presented in the Company's response to clarification question B8, two clinical experts noted they would expect patients that receive ribociclib plus AI to have a reduced proportion of DR and NMR events versus SPM and death events, as per the mechanism of action of ribociclib plus AI. As such, the statement "*there is insufficient evidence*" may be considered misleading, given there is evidence available in the form of clinical validation.			overlap substantially, indicating that there is insufficient statistical evidence of a difference between the iDFS event distributions based on treatment. … The EAG highlights that this EAG revision does not result in equal transition probabilities (or equal efficacy) for the two treatments since the underlying probabilities of experiencing any iDFS event differ between the two treatments (Table 35). This aligns with clinical advice to the company that they would expect patients that receive ribociclib+AI to have a reduced proportion of DR and NMR events versus ET (company response to clarification question B8).

Issue 8 Reporting of clinical benefit of ribociclib

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment

Page 42, Section 3.3.1; Page 60, Section 3.7.1 of the EAG report describes the magnitude of clinical benefit of ribociclib plus AI vs AI as "*modest*" in terms of iDFS, RFS and DDFS. Specifically, the report states in reference to the April 2024 data cut of NATALEE that "*the differences in iDFS, RFS and DDFS event rates between the ribociclib+AI and AI arms were modest.*" The Company highlight that the use of the word "*modest*" to describe the clinical benefit of ribociclib plus AI is misleading and downplays the benefit of ribociclib plus AI in this indication. "*Modest*" infers that the benefit is small. In contrast, the benefit of ribociclib plus AI over AI (particularly for iDFS) is not only statistically significant, but is also clinically meaningful. This is evidenced by the ESMO Magnitude of Clinical Benefit Scale which ranks the magnitude of clinical benefit for new approaches to adjuvant therapy or new	To remove use of the word "*modest*" when describing the clinical benefit of ribociclib.	To provide a more accurate representation of findings from the NATALEE trial (with respect to iDFS, RFS and DDFS), and thus the clinical benefit of ribociclib plus AI in this indication.	This is not a factual inaccuracy. No change required to the EAG report.

potentially curative therapies from A–C, with 'A' being the highest grade. Notably, ribociclib plus AI received an ESMO MCBS score of 'A' based on the iDFS primary endpoint results of the NATALEE trial, demonstrating the clinically significant benefit of ribociclib plus AI in this setting. As such, the Company requests that the use of the word "*modest*" to describe the clinical benefit of ribociclib plus AI is removed from the report, to provide a more accurate representation of the NATALEE trial findings.			

Issue 9 Reference to the use of ET

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 56, Section 3.4.7 of the EAG report states that "*only patients who **are not** eligible for treatment with abemaciclib+ET would be treated with ET, i.e., Population 5.*" It is factually	Amend wording such that it is captured that some patients eligible for abemaciclib plus ET would receive ET.	To ensure fair representation and reporting of clinical practice.	Text amended as follows: The EAG cautions that these results have been generated using data from patients who are eligible for treatment with

incorrect to state that *only* patients ineligible for abemaciclib+ET would receive ET. Some patients eligible for abemaciclib+ET may still receive ET in clinical practice, e.g. due to patient choice and contraindications, as noted by one UK clinical expert consulted by the Company during the November 2023 advisory board (see Appendix Q.2 of the Company-submitted appendices).			abemaciclib+ET. In the NHS, most patients who are eligible for treatment with abemaciclib+ET would be treated with abemaciclib+ET, not ET. The EAG considers that Population 5 is the most relevant population for the comparison of ribociclib+AI versus ET because all NHS patients who are not eligible for treatment with abemaciclib+ET would be treated with ET.

Issue 10 Reporting of subgroup cost-effectiveness evidence presented by the Company

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Table 26, Page 64, Section 4.2.1 of the EAG report notes that "*The company has not provided cost effectiveness for the group of patients who are not eligible for abemaciclib+ET; this is a relevant patient group.*" While not factually inaccurate, the Company propose that it would be useful and fair to provide extra context to this	Update the wording within Table 26, Page 64, Section 4.2.1 to note the wider context that the "abemaciclib-ineligible population" subgroup was not requested by NICE in the final scope.	To provide transparency on the CS's alignment with the NICE draft or final scope.	Text amended as follows: The company has not provided cost effectiveness for the group of patients who are not eligible for abemaciclib+ET; this is a relevant patient group. However, the EAG acknowledges that this subgroup was not specified

section of the EAG report that the “abemaciclib-ineligible population” subgroup was not requested in the NICE final scope.			in the final scope issued by NICE.

Issue 11 Overestimation of AE costs included by the EAG

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Table 27, Page 65, Section 4.2.1, and Table 39, Page 89, Section 6.5 of the EAG note the AEs in the model were poorly costed and suggest alternative AE costs. The Company would like to highlight the EAG’s costs for AEs, particularly neutropenia, are considerably higher than the cost used in previous appraisals in breast cancer. In TA810 (abemaciclib+ET for HR+, HER2-negative, node-positive early breast cancer at high risk of recurrence), the cost of neutropenia was modelled as £200.20 for the cost of one medical oncology consultant led outpatient	The Company request the EAG change the AE costs, particularly for neutropenia, to be more reflective of the costs used in previous appraisals.	The EAG cost for neutropenia is not in line with previous appraisals in similar indications.	The EAG has updated the cost of neutropenia to £192.95 (National Schedule of NHS Costs 2023/24: HRGs: WF01A Medical oncology (service code: 370) non-admitted face to face attendance follow up.

appointment. This approach was accepted in TA810 and is in line with the approach used in the Company's model. Furthermore, in TA992 (trastuzumab deruxtecan for treating HER2-low metastatic or unresectable breast cancer after chemotherapy), the cost of neutropenia was modelled as £761.01, which is considerably lower than the EAG's cost of £2,174. The EAG note higher costs were included in their model on the assumption that all Grade ≥3 AEs require hospitalisation. However, in TA992, the clinical experts highlighted that neutropenia would only require admission if accompanied by fever or other signs of sepsis, and therefore the cost of £761.01 used in that appraisal was considered an overestimate. It is therefore extremely likely the EAG's cost of £2,174 for neutropenia is inappropriate as it greatly overestimates the costs associated with neutropenia.			

Issue 12 Inaccurate description of the sources for transition probabilities

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 68, Section 4.7 of the EAG describes the source of the transition probabilities incorrectly with the current wording "*Transition probabilities to and from all other health states (except within and out of the DR state) are taken from the literature.*" Likewise, Page 69, Section 4.7.4 of the EAG report states that "*Transition probabilities out of the NMR and remission health states were derived from the literature or assumptions*" which is also inaccurate. The transition probabilities from the NMR health state to death and from the remission health state to death were based on the iDFS event rate from NATALEE, or general population mortality, whichever is higher (see Table 45 of CS).	Clarify the derivation of the transition probabilities in the model, based on Table 45 of the CS.	To maintain accuracy regarding the source of the transition probabilities incorporated into the CS model.	Text amended as follows: Section 4.7, p68 Transition probabilities to and from all other alive health states (except within and out of the DR state) are taken from the literature. Transition probabilities into the death health state (except from the DR state) were assumed to be equal to the iDFS mortality rate or background mortality rate, whichever was higher. Section 4.7.4, p69 Transition probabilities out of the NMR and remission health states into other alive health states were derived from the literature or assumptions. Transition probabilities into the death health state were assumed to be equal to the iDFS mortality rate or

			background mortality rate, whichever was higher.

Issue 13 Inaccurate description of approach to modelling wastage

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 72, Section 4.8.1 of the EAG report states that "*Wastage is included for treatment with abemaciclib to account for down-dosing due to AEs. No wastage is included for other treatments.*" However, as per the Company's response to clarification question B9, additional wastage assumptions were incorporated into the Company's revised base case economic analyses for all populations, and therefore this statement no longer holds true. Specifically, in response to clarification question B9, the Company noted that it may also be appropriate to	Update this section on drug wastage to acknowledge that, in addition to wastage being included for treatment with abemaciclib to account for down-dosing due to AEs, wastage due to reasons other than down-dosing for both ribociclib and abemaciclib was also included in the Company's base case economic analyses.	To maintain accuracy of the reporting of the Company approach to drug wastage.	Text amended as follows: Section 4.8.1, p72 Wastage is also included for both ribociclib and abemaciclib to account for unused whole packs of medication.

consider wastage due to reasons other than down-dosing for both ribociclib and abemaciclib, in addition to the down-dosing wastage assumption considered relevant for abemaciclib in the CS.			

Issue 14 Inaccurate description of the approach to modelling efficacy in the ET arm

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Table 33, Page 78, Section 6.1 of the EAG report states "*The company has assumed that the efficacy of ET is the same as the efficacy of AI*." This description is inaccurate because in the Company economic model, data from the control arm of the NATALEE trial (which included only AIs) is adjusted by applying a weighted HR to account for the decreased efficacy of tamoxifen.	Update the sentence to clarify ET is not assumed equal to AI within the cost-effectiveness model.	To maintain accuracy between the Company base case and the EAG report.	Text amended as follows: Section 6.1, Table 33 The company has assumed that the efficacy of ET is the same as the efficacy of AI adjusted for lower expected efficacy of tamoxifen; for the purposes of the economic evaluation, clinical advice to the EAG is that this approach is reasonable.

Issue 15 Justification of the curve choices in the DR state

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 83, Section 6.4.1 of the EAG report, the EAG note it is not appropriate to apply hazard ratios to loglogistic and lognormal curves. The Company acknowledge that the EAG's approach here is technically correct, however, the approach adopted by the Company is common practice in economic modelling and does not inherently lead to inaccurate predictions. It is important that the clinical validity of the chosen curves is considered alongside this technical consideration.	The Company propose the EAG acknowledge that the Company's approach is an accepted modelling approach, and add context relating to the importance of clinical validity of the chosen curves.	Whilst the application of hazard ratios to loglogistic and lognormal curves can be associated with some limitations, the Company believe it is more important for the curve choices to be clinically valid.	This is not a factual inaccuracy. No change required to the EAG report. Note that, as stated in Section 6.4.1, p85, "[c]linical advice to the EAG is that curves chosen by the EAG generate plausible long-term PFS and OS estimates for both DR substates."

Issue 16 Reporting of clinical advice to the Company

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 86, Section 6.4.2 of the EAG report states that the EAG scenario where [redacted]% of ET-resistant CDK4/6 inhibitor-	Amend the wording on Page 86, Section 6.4.2 of the EAG report to acknowledge that only one clinical expert was of the opinion that most patients would be	To maintain factual accuracy of reporting of clinical advice to the Company.	Text amended as follows: Section 6.4.2, p87

sensitive patients are retreated with a CDK4/6 inhibitor "*aligns with expert advice to the company that most patients would be retreated with a CDK4/6 inhibitor*." The Company consider the EAG's wording to be misleading as it implies that <u>all</u> clinical experts consulted by the Company considered that most patients would be retreated with a CDK4/6 inhibitor. However, as reported in Q.3 of the Company-submitted appendices, only one clinical expert (out of six) was strongly of the opinion that they would rechallenge with a CDK4/6 inhibitor for the majority of patients, while another clinical expert suggested that CDK4/6 inhibitor usage among patients treated with CDK4/6 inhibitors in the adjuvant setting would be low compared to those that received adjuvant ET monotherapy. The remaining clinical experts felt it was unclear how the update to the NHS Blueteq form will impact	retreated with a CDK4/6 inhibitor, for example "*This scenario also aligns with <u>one clinical expert's</u> advice to the company that most patients would be retreated with a CDK4/6 inhibitor*".		The majority of clinical advice to the company was that, although the NHS Blueteq form has been updated to allow retreatment of patients who received a CDK4/6 inhibitor in the adjuvant setting, it is too early to know how this change would impact prescribing … One clinician considered that most eligible patients would be retreated with a CDK4/6 inhibitor whilst another considered that CDK4/6 inhibitor use would be lower for ET-resistant CDK4/6 inhibitor-sensitive patients than for patients who had received adjuvant ET alone. Another clinician considered that most patients would be retreated with a CDK4/6 inhibitor. … In the EAG scenario, the proportion of ET-resistant CDK4/6 inhibitor-sensitive patients retreated with a CDK4/6 inhibitor is equal to the proportion of patients receiving a CDK4/6

prescribing as they have not yet had patients that meet these criteria given adjuvant abemaciclib has only been available in the NHS since 2022.			inhibitor following adjuvant ET alone. This assumption aligns with the advice of one expert to the company that most patients would be retreated with a CDK4/6 inhibitor.

Issue 17 Inaccurate reporting of Company clarification base case results

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Tables 43, 45 and 47 on Pages 91–93 of Section 6.6 of the EAG report incorrectly report the NMB for the probabilistic pairwise results from the Company clarification base case.	Please could the NMB reported be amended to the following: Table 43: £16,186 Table 45: £43,350 Table 47: £22,214	To maintain accuracy of the results reported from the Company's clarification question model.	Values have been amended in the EAR tables.
Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG comment**
The EAG's base case probabilistic results in Tables 43, 45 and 47 of Pages 91–93 of Section 6.6 of the EAG report are unreliable because the inputs for the PSA were not correctly updated. The	The EAG have implemented various model updates but failed have not to correctly updated the PSA inputs on the 'PA Inputs' tab related to these changes, leading to unreliable probabilistic results in Tables 43, 45 and 47 in the EAG report. These results should not be used for inference. The changes required to the PSA inputs tab have been discussed in	To ensure the EAG CEM produces reliable probabilistic results.	Values have been amended in the EAR tables.

results should not be used for inference.	detail in 'EAG Modelling Inaccuracies' section below.		

Minor factual inaccuracies

Issue 18 Reporting of ribociclib formulation

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 20, Section 2.2.2 of the EAG report states that ribociclib is available as 200 mg and 400 mg tablets – this is incorrect. As per the SmPC for ribociclib, ribociclib is only available as 200 mg film-coated tablets. To achieve the desired dose of 400 mg in early breast cancer, patients must take 2 x 200 mg tablets.	Amend the wording to state that ribociclib is available as 200 mg tablets.	To maintain factual accuracy regarding the composition of available ribociclib tablets.	Text amended as suggested.

Issue 19 Reference to EMA approval of ribociclib in early breast cancer

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 21, Section 2.2.2 of the EAG report, the following statement "*European Medicines Agency (EMA) approval was received in November 2024*" is referenced incorrectly. The current reference is the SmPC for abemaciclib, whereas it should refer to the SmPC for ribociclib.	Update the provided reference to be the current published ribociclib SmPC.	Incorrect reference provided.	The incorrect reference has been replaced with the following reference: European Medicines Agency. Kisqali. Procedural steps taken and scientific information after authorisation. Published 18 December 2024; Available from: https://www.ema.europa.eu/en/documents/procedural-steps-after/kisqali-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf. Accessed 6 February 2025.

Issue 20 Reference to MHRA approval of ribociclib in early breast cancer

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 21, Section 2.2.2; Table 1, Page 24, Section 2.4 of the EAG report notes that Medicines and Healthcare products Regulatory Agency approval is expected in [redacted]	Update the anticipated Medicines and Healthcare products Regulatory Agency approval date to [redacted].	To report an up-to-date anticipated Medicines and Healthcare products Regulatory Agency approval date.	Text amended as suggested.

[redacted].Whilst this is accurate reporting of the anticipated approval date provided in the CS, the Company would like to highlight that Medicines and Healthcare products Regulatory Agency approval is now anticipated for [redacted].			

Issue 21 Reporting of monarchE ET arm

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 28, Section 2.4.4 of the EAG report states that the available ET therapies in monarchE were "*anastrozole, letrozole, and tamoxifen*". This is incorrect. The ET arm of monarchE comprised tamoxifen, toremifene, letrozole anastrozole or exemestane; with or without ovarian suppression, as highlighted in Section 3.4.1 of the EAG report. The wording in Section 2.4.4 of the EAG report should therefore be updated to reflect this.	Update the wording on Page 28, Section 2.4.4. of the EAG report to clarify that the ET arm of the monarchE comprised tamoxifen, toremifene, letrozole anastrozole or exemestane; with or without ovarian suppression.	To maintain factual accuracy of the comparator arm (i.e. ET arm) of the monarchE trial.	Text amended as follows: In the monarchE trial,[12] available ET therapies were anastrozole, letrozole, exemestane, and tamoxifen and toremifene, with or without ovarian suppression

Issue 22 Interpretation of results (proportion of patients discontinuing treatment)

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Table 8, Page 39, Section 3.2.4 of the EAG report states that "*A slightly higher*	The EAG comment in Table 8 of the EAG report should be amended to the following "*A slightly lower proportion of patients in*	Value for discontinuation in the ribociclib plus AI arm of NATALEE, in addition to subsequent interpretation, should	Text amended as suggested.

proportion of patients in the ribociclib+AI arm ([redacted] discontinued treatment than in the AI arm ([redacted] (see NATALEE trial CSR [29 April 2024 DCO],[11] Table 1-2)", which is incorrect. Table 1–2 of the NATALEE trial CSR (April 2024 data cut) reports that [redacted]%) of patients in the ribociclib plus AI arm discontinued treatment. Therefore, a lower proportion of patients in the ribociclib plus AI arm discontinued treatment than in the AI arm [redacted]	*the ribociclib+AI arm [redacted] discontinued treatment than in the AI arm ([redacted] (see NATALEE trial CSR [29 April 2024 DCO],11 Table 1-2).*"	be corrected as per Table 1–2 of the NATALEE trial CSR (April 2024 data cut).	

Issue 23 Reporting of data (median follow-up)

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Table 11, Page 43, Section 3.3.2 of the EAG report states that the median follow-up for Population 2 in the NATALEE trial is not reported. This is incorrect as per Figure 21 on Page 83 of the CS, which depicts that the median follow-up for this population at the	The median follow-up for Population 2 (NATALEE node-positive, high-risk) in Table 11 of the EAG report should be updated to 44.2.	Value should be provided as per Figure 21 of the CS.	Text amended as suggested.

April 2024 data cut was 44.2 months.			

Issue 24 Alignment of quality assessment reporting

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
In Table 14, Page 47, Section 3.4.2 of the EAG report the EAG determines that the risk of bias for "*Were the care providers, participants and outcome assessors blind to treatment allocation?*" was unclear. This was based on the monarchE trial being open-label with outcomes that were investigator-assessed, although the secondary outcome OS is an objective measure that is not subject to bias. The EAG note that the primary outcome, other secondary outcomes and safety outcomes may be subject to bias. While the Company believes this a fair assessment of the risk of bias for this quality assessment item, the	The EAG assessment of risk for the "*Were the care providers, participants and outcome assessors blind to treatment allocation?"* should be consistent between the monarchE and NATALEE trials, given their similarities in design.	To maintain consistency in the approach to quality assessment for the monarchE and NATALEE trials.	Text amended as suggested.

Company note that the EAG record the risk level as high for the equivalent risk assessment for NATALEE (Table 8, Page 39, Section 3.2.4 of the EAG report). This is despite the NATALEE trial having the same considerations as the monarchE trial (i.e. open-label, investigator-assessed outcomes, objective secondary outcome in OS, and other outcomes potentially being subject to bias).			

Issue 25 Reporting of Company clarification question responses

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 60, Section 3.7.2 of the EAG report states that "*The company has only generated STC results for the comparison of ribociclib+AI versus abemaciclib+ET (Population 4).*" which is referred to as a minor concern. The Company would like to clarify that during the clarification stage, only STC	Amend wording to state that only the STC results for the comparison of ribociclib+AI versus abemaciclib+ET (Population 4) was requested at clarification questions.	To maintain accuracy regarding the data requested of the Company and the data provided by the Company.	Text amended as follows. The EAG only requested (clarification question A9) STC results for the comparison of ribociclib+AI versus abemaciclib+ET (Population 4). This is a minor concern as Population 5 is the most representative of NHS patients who would be

results for ribociclib plus AI versus abemaciclib plus ET was requested by the EAG, and therefore the Company fulfilled this request.			treated with ET and direct trial evidence for the comparison of ribociclib+AI versus AI is available from the NATALEE trial.

Issue 26 Inaccurate descriptions of the approach to modelling waning

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 69, Section 4.7.3 of the EAG report states "*treatment effect waning for treatment with ribociclib+AI (and abemaciclib+ET) is implemented from 8 years and reaches the background hazard rate at around 30 years.*" The timepoint quoted for when iDFS hazard rate equals the hazard rate for the general population is incorrect. For the ITT population, this timepoint is 25.2 years.	Correct the timepoint reported to "*around 25 years*".	To maintain accuracy between the Company base case and the EAG report.	Text amended as suggested.
Page 69, Section 4.7.3 of the EAG report states "*The distribution of iDFS events for ribociclib+AI and abemaciclib+ET is set to equal*	Update this sentence to "*The distribution of iDFS events in the ribociclib+AI and abemaciclib+ET arms linearly approaches the distribution for ET such that they are equal at the end of the waning period*."	To maintain accuracy of the description of the approach to treatment waning implemented in the model.	Text amended as suggested.

the distribution of iDFS events for ET from the initiation of treatment effect waning." Please could the EAG revise this sentence to reflect the description provided in clarification question B.6.			
Page 83, Section 6.3.3 of the EAG report states "*Ribociclib+AI iDFS hazard rates are equal to general mortality rates at 27 years for Population 1 and equal to 29 years for Population 4*." The timepoint quoted for when iDFS hazard rate equals the hazard rate for the general population is incorrect.	Please could the correct timepoints of 25 and 27 years be reported.	To maintain accuracy between the Company clarification question model and the EAG report describing this model.	Text amended as suggested.

Issue 27 Inaccurate description of approach to modelling TTD

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 72, Section 4.8.1 of the EAG report states "*Estimates of TTD for ET alone were assumed to be the same as for AI in combination with ribociclib*."	Please could the EAG update this sentence to "*Estimates of TTD for ET alone were estimated from parametric curves fitted to post-matching and weighted NATALEE-trial TTD K-M data for the AI alone arm."*	To maintain accuracy of the description to modelling TTD in the economic model.	Text amended as suggested.

This description of the approach to modelling TTD for patients in the ET alone arm is incorrect, as separate TTD extrapolations were fitted to data from NATALEE in the control arm to inform this.			

Issue 28 Missing disease characteristic included in the MAIC

Description of problem	Description of proposed amendment	Justification for amendment	
Table 48, Page 99, Section 8.1 (Appendix 1) of the EAG report lists the unique baseline patient demographic and disease characteristics that were included in the primary MAIC. The list provided is missing "*Pathologic tumour size (cm)*" which, in addition to the other eighteen characteristics listed, was included in the primary MAIC.	Update the list of baseline patient demographic and disease characteristics to also include "*Pathologic tumour size (cm)*", in addition to the characteristics currently listed.	To maintain accuracy regarding the characteristics included in the Company primary MAIC.	Text added to Table 48 (Table 49 in updated EAR) as suggested. (Tumour size was already listed in Table 15)

Issue 29 Reporting of data (monarchE baseline characteristics)

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG comment</th></tr>
<tr>
<td>Table 49, Page 105, Section 8.2.2 of the EAG report, the data for the ECOG PS score and the corresponding labels are reported incorrectly.

As per Table 16 of the Company-submitted appendices, the possible ECOG PS scores are 0, 1, 2, 3 or missing. As such the ECOG PS categories in Table 49 of the EAG report of (0; 1; 3, 4 and missing) are incorrect. The correct labelling, using the EAG's grouping approach would be as follows:

• 0
• 1
• 2, 3, and missing

Additionally, the data for the ET arm in monarchE, category "3, 4, and missing"</td>
<td>The following updates should be made to Table 49 of the EAG report, with regards to presented ECOG PS categories and data.

<table>
<tr><th></th><th colspan="2">monarchE (Cohort 1)</th></tr>
<tr><th>ECOG PS</th><th>Abemaciclib+ET (N=2,555)</th><th>ET (N=2,565)</th></tr>
<tr><td>0</td><td>85.4%</td><td>83.7%</td></tr>
<tr><td>1</td><td>14.5%</td><td>16.1%</td></tr>
<tr><td>2, 3, and missing</td><td>0.1%</td><td>0.2%</td></tr>
</table>
</td>
<td>Values should be provided as per Table 16 of the Company-submitted appendices.</td>
<td>Text amended as follows</td>
</tr>
</table>

is incorrect, and should be updated to 0.2%.			

Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Table 3, Page 27, Section 2.4.2 of the EAG report includes a typographical error when referring to Population 4a. The current population label is "*Population 4/4a*".	Correct the labelling of this population from "*Population 4/4a (NATALEE trial selected, unweighted population; data used in the direct clinical effectiveness comparison)*" to "*Population 4a (NATALEE trial selected, unweighted population; data used in the direct clinical effectiveness comparison)*."	Update the typographical error to ensure accuracy of population labelling.	This was not a typographical error, however, text amended as suggested.
Table 3, Page 27, Section 2.4.2 of the EAG report, the ESS for Population 4b (NATALEE trial selected, reweighted population; data used in the indirect clinical effectiveness comparison) is incorrect. After weighting, the ESS for the ribociclib plus AI and ET arms were [redacted] and [redacted], respectively, as stated on page 94 of the CS; as such, the total ESS is [redacted].	The ESS of patients in Population 4b should be [redacted]	The value should be corrected as per page 94 of Document B of the CS. The ESS should also be marked as CiC given these data are not intended to be published.	Text amended as suggested.

The ESS values should also be marked as CiC given these data are not intended to be published.			
Table 7, Page 38, Section 3.2.3 of the EAG report includes a typographical error in the heading for the AI arm of Population 4. The current heading is "*Characteristic*".	Correct the heading for the Population 4, AI arm heading from "*Characteristic*" to "*AI (n=[redacted])*".	Update the spelling of the typographical error to ensure correct heading.	Text amended as suggested.
Page 48, Section 3.4.4 of the EAG report states the proportion of patients with tubular breast cancer in the ET arm of monarchE Cohort 1 to be [redacted]%. As per Table 16, Page 167 of the Company-submitted appendices, this value is incorrect and should be ***%.	Correct the proportion of patients with tubular breast cancer in the ET arm of monarchE Cohort 1 from "*[redacted]%*" to *[redacted]%".*	To ensure the accuracy of the report.	Text amended as suggested.
Table 16, Page 50, Section 3.4.5 of the EAG report reports the reduction of Population 4 sample size post-weighting incorrectly. As per Table 31, Page 95 of the CS, the percent change in sample size for the ribociclib plus AI arm is [redacted]%, while the	Correct the reduction in sample size for ribociclib plus AI to [redacted]%. Correct the reduction in sample size for AI to [redacted]%.	To ensure the accuracy of the report.	Text amended as suggested.

percent change in sample size for the AI arm is [redacted]%. The EAG report reports these values the other way round.			
Page 70, Section 4.7.5 and Page 83, Section 6.4.1 of the EAG report include typographical errors when referring to MONALEESA-2 and MONALEESA-3. The current wording on Page 70, Section 4.7.5 is as follows: "*MONALEESA-2[27] (ET-resistant) and MONALEESA-3[28] (ET-sensitive)*" The current wording on Page 83, Section 6.4.1 is as follows: "*Outcomes (PFS and OS) for the treatment baskets were estimated by fitting parametric PFS and OS curves for ribociclib+fulvestrant (ET-resistant DR substate) or ribociclib+NSAI (ET-sensitive DR substate) to patient-level data from the MONALEESA-2[27]and MONALEESA-3[28] trials, respectively*."	On Page 70, Section 4.7.5, correct the labelling of the trials from "*MONALEESA-2[27] (ET-resistant) and MONALEESA-3[28] (ET-sensitive)*" to "*MONALEESA-2[27] (ET-sensitive) and MONALEESA-3[28] (ET-resistant)*" On Page 83, Section 6.4.1, correct the wording to "*Outcomes (PFS and OS) for the treatment baskets were estimated by fitting parametric PFS and OS curves for ribociclib+fulvestrant (ET-resistant DR substate) or ribociclib+NSAI (ET-sensitive DR substate) to patient-level data from the MONALEESA-3[28]and MONALEESA-2[27] trials, respectively*."	Swap the ET-sensitive and ET-resistant labelling to ensure accuracy of trial descriptives.	Text amended as suggested.

Page 72, Section 4.8.1 of the EAG report includes a typographical error in the spelling of ribociclib. The current spelling is as follows: "*ribocicilib*".	Correct the spelling of "*ribocicilib*" to "*ribociclib*".	Update the spelling of the typographical error to ensure correct drug name.	Text amended as suggested.
Page 73, Section 4.8.1 of the EAG report, the RDI multiplier for treatment with abemaciclib in Population 4 ([redacted] is reported incorrectly. The reported RDI multiplier for abemaciclib corresponds to the RDI multiplier in the CS. However, at clarification questions the Company identified an error in the methodology used to determine the RDI for ribociclib due to treatment holds, which informs the RDI for adjuvant abemaciclib (as part of abemaciclib plus ET). As such, the Company presented the revised calculation for determining RDI due to treatment holds, which equated to an RDI for abemaciclib of [redacted] (see Company response to clarification question B9).	Revise the RDI multiplier for treatment with abemaciclib in Population 4 to [redacted] to align with revised calculations presented in response to clarification question B9.	To maintain accuracy regarding the reported RDI multiplier for treatment with abemaciclib in Population 4.	Text amended as suggested.

Page 73, Section 4.8.1 of the EAG report, the reporting of the RDI multipliers for AIs in combination with ribociclib and the RDI multipliers for ET in Population 1 (NATALEE ITT) is incorrect, as is the reporting of the assumptions. Specifically, the RDI multipliers for AIs in combination with ribociclib and for ET have been swapped. As per Table 58 of the CS, in Population 1 (NATALEE ITT) the RDI multipliers for AIs in combination with ribociclib are as follows: anastrozole=[redacted]%, letrozole=[redacted]% and goserelin=[redacted]%). The assumptions are that exemestane equal to anastrozole and letrozole, zoledronic acid=[redacted]%). Likewise, as per Table 58 of the CS, in in Population 1 (NATALEE ITT) the RDI multipliers for ET are as follows: anastrozole=[redacted]%, letrozole=[redacted]% and goserelin=[redacted]%. The assumptions are that exemestane equal to	The RDI multipliers for AIs in combination with ribociclib should be updated to: • Anastrozole=[redacted]% (sourced from NATALEE ITT) • Letrozole=[redacted]% (sourced from NATALEE ITT) • Exemestane=[redacted]% (assumed equal to anastrozole and letrozole) • Goserelin=[redacted]% (sourced from NATALEE ITT) • Zoledronic acid=[redacted]% (assumption) The RDI multipliers for ET should be updated to: • Tamoxifen=[redacted]% (assumption) • Letrozole=[redacted]% (sourced from NATALEE ITT) • Anastrozole=[redacted]% (sourced from NATALEE ITT) • Exemestane=[redacted]% (assumption) • Goserelin=[redacted]% (sourced from NATALEE ITT) • Zoledronic acid=[redacted]% (assumption)	To ensure accuracy of the RDI multipliers in the report.	Text amended as suggested.

anastrozole and letrozole, tamoxifen=[redacted]%, zoledronic acid=[redacted]%).			
Table 35, Page 84, Section 6.4.1 of the EAG report notes the landmark survival in the ET-resistant health state for OS using the Company's base case curve at 5, 10, 20 and 30 years as [redacted]%, [redacted]%, [redacted]% and [redacted]%. The Company believe this row has been reported incorrectly.	Amend the data in Table 35 for OS in the ET-resistant health state using the Company's base case curve to be [redacted]%, [redacted]%, [redacted]% and [redacted]%.	To maintain accuracy between the model and EAG report.	Text amended as suggested.
Table 41, Page 90, Section 6.4.3 of the EAG report includes typographical errors when referring to "*Letr**a**zole*", "*Anastr**a**zole*" and "*Gosrelin*".	Please could the EAG correct the spelling errors in this table.	To ensure the accuracy of the report.	Text amended as suggested.

EAG modelling inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
The EAG's base case probabilistic results in Tables 43, 45 and 47 of Pages	The EAG have implemented various model updates but have not correctly updated the PSA inputs on the 'PA Inputs' tab related to these changes, leading to unreliable probabilistic	To ensure the CEM produces reliable probabilistic results when the EAG base	The model and the model revision instructions (EAR, Appendix 8.3) have

91–93 of Section 6.6 of the EAG report can be considered unreliable because the inputs were not correctly updated. The results should not be used for inference.	results in Tables 43, 45 and 47 of Section 6.6 in the EAG report. These results should not be used for inference. All the specified changes below should be implemented using IF functions, ensuring they only activate when the associated revision setting on the 'Results' tab equals 1. These changes should be applied to all populations. To save the changes to each population's 'PA Inputs' tab, click the 'Load/Save' button, select 'Save Scenario', and then save the relevant population. This ensures the changes are stored properly. The specific PSA input issues are: **EAG Revision 1 Adjust proportion of patients moving from iDFS to other health states:** When the EAG's revision is applied, Cells G155:G158 on the 'PA Inputs' tab should equal 'Link' and Cells F155:F158 on the 'PA Inputs' tab should equal the named ranges as follows: • F155: '_psa_comp1.idfs_death_1' • F156: '_psa_comp1.idfs_dr_1' • F157 : '_psa_comp1.idfs_spm_1' • F158: '_psa_comp1.idfs_nmr_1' **EAG Revision 3 Adjust treatment mix in ET-resistant DR substate:** When the EAG's revision is applied, the ET-resistant DR substate treatment mix sample size inputs for the Dirichlet distribution in Cells L2105:L2111 and L2127:L2133 on the 'PA Inputs' tab should equal:	case settings are applied.	been updated to reflect these comments.

	Ribo + AI: • L2105: 0.00 • L2106: 30.00 • L2107: 60.00 • L2108: 0.70 • L2109: 3.85 • L2110: 1.75 • L2111: 0.70 Abe + ET: • L2127: 60.00 • L2128: 30.00 • L2129: 0.00 • L2130: 0.70 • L2131: 3.85 • L2132: 1.75 • L2133: 0.70 **EAG Revision 4 Adjust treatment mix in ET-sensitive DR substate:** When the EAG's revision is applied, the ET-sensitive DR substate treatment mix sample size inputs for the Dirichlet		

	distribution in Cells L1892:L1895 and L1914:L1917 on the 'PA Inputs' tab should equal: • L1892 and L1914: 40.00 • L1893 and L1915: 10.00 • L1894 and L1916: 40.00 • L1895 and L1917: 10.00 **EAG Revision 5 Change ET-sensitive health state utility values:** When the EAG's revision is applied, Cell G2049 on the 'PA Inputs' tab should equal 'Link' and F2049 should equal '_psa_comp1.util_nmr'.		
Cell G30 'Utilities State' tab in the CEM for Population 1.	The EAG have only applied their preferred ET-sensitive utility value to the ET arm of the model for Population 1. The formula in Cell G30 of the 'Utilities State' tab should be updated to: = _input_comp2.util_et_sens_pfs	To ensure the CEM produces reliable deterministic results when the EAG base case settings are applied.	The model and the model revision instructions (EAR, Appendix 8.3) have been updated to reflect these comments.
Cells E20 on the 'Efficacy ET Resist' and Efficacy ET Sensitive' tabs in the CEM for all populations.	The EAG have correctly implemented their preferred PFS and OS curves for the ET-sensitive and ET-resistant health states, however, the Company would like to highlight to the EAG the TTD curve for add-on therapies should also be updated to align with the EAG's preferred PFS curve to maintain the assumption used in the model that PFS=TTD in the DR state. The formulae in Cells E20 on both 'Efficacy ET Resist' and Efficacy ET Sensitive' tabs should be updated to '=_input_et_res_2.dist_1' and '=_input_et_sens_2.dist_1' to	To maintain the assumption used in the model that PFS=TTD in the DR state.	The model and the model revision instructions (EAR, Appendix 8.3) have been updated to reflect these comments.

	ensure the TTD curves are automatically updated to align with the chosen PFS curve.		
Page 108, Section 8.3 (Appendix 3).	The calculations for EAG Scenarios 1 and 2, where the treatment waning start and end times are set in Cells L1057 and S1057 on the 'Database' tab, are currently incorrect. The end treatment waning time ('EAGTxWaneEnd') is mistakenly applied as the duration of waning, instead of the end time. The formulae in Cells L1057 and S1057 on the 'Database' tab should be updated as follows: • Current formula: IFS(EAGScen1=0,('Efficacy Waning'!$I$11-comp1.wane_idfs_start), AND(EAGScen1=1,EAGTxWaneEnd<=EAGTxWaneStart),('Efficacy Waning'!$I$11-comp1.wane_idfs_start), AND(EAGScen1=1,EAGTxWaneEnd>EAGTxWaneStart),**EAGTxWaneEnd*12**) • Updated formula: IFS(EAGScen1=0,('Efficacy Waning'!$I$11-comp1.wane_idfs_start), AND(EAGScen1=1,EAGTxWaneEnd<=EAGTxWaneStart),('Efficacy Waning'!$I$11-comp1.wane_idfs_start), AND(EAGScen1=1,EAGTxWaneEnd>EAGTxWaneStart), **EAGTxWaneEnd*12-comp1.wane_idfs_start)** This correction ensures that the treatment waning end time is correctly applied as the end point (e.g., from Year 5 to Year 8 in Scenario 1), rather than incorrectly applying it as the duration	To ensure the CEM produces reliable deterministic results when the EAG base case settings are applied.	The model and the model revision instructions (EAR, Appendix 8.3) have been updated to reflect these comments.

	(e.g., from Year 5 to Year 13), aligning with the scenario's description.		
'DSA Inputs' tab in the CEM for all populations.	Changes made by the EAG in the CEM must be reflected in the 'DSA Inputs' tab. The inputs related to the EAG's revisions should be updated in the lower and upper bounds on the 'DSA Inputs' tab for each population to ensure the DSA results are reliable. All the specified changes should be implemented using IF functions, ensuring they only activate when the revision setting on the 'Results' tab equals 1. To save the changes to each population's 'DSA Inputs' tab, click the 'Load/Save' button, select 'Save Scenario,' and then save the relevant population. This ensures the changes are stored properly.	To ensure the CEM produces reliable DSA results when the EAG base case settings are applied.	The model and the model revision instructions (EAR, Appendix 8.3) have been updated to reflect these comments.

Confidentiality highlighting inaccuracies

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG comment
Table 3, Page 27, Section 2.4.2	The number of patients in Population 4/4a should be marked as confidential as these data are not intended to be published.	Population 4/4a (NATALEE trial selected, unweighted population; data used in the direct clinical effectiveness comparison): [redacted])	Text amended as suggested.

<table>
<tr>
<td>Page 28, Section 4.4.4</td>
<td>The number of patients in Population 4/4a should be marked as confidential as these data are not intended to be published.</td>
<td>“Over half of NATALEE trial Population 1 ([redacted] patients, [redacted]%) would, if treated in the NHS, be eligible for treatment with abemaciclib+ET, as per the NICE TA810[9] recommendation.”</td>
<td>Text amended as suggested.</td>
</tr>
<tr>
<td>Table 7, Page 37–38, Section 3.2.3</td>
<td>The baseline characteristics for Population 4 and Population 5 should be marked as confidential as these data are not intended to be published.

The data in the “Other” category for Race in Population 1 (in addition to Population 4 and 5) should be marked as confidential. This category has been formed by the EAG by combining “Other”, “Native Hawaiian or Other</td>
<td>All data for Population 4 and Population 5, including the N= values marked as CiC.

In addition, please also apply highlighting to the “Other” category of Race in Population 1 as follows:

<table>
<tr><td>Other</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td>
<td>Text amended as suggested.</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td>Pacific Islander” and “American Indian or Alaska Native” data from Table 9 of the CS, which were marked as confidential as these data are not intended to be published.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Table 12, Page 44, Section 3.3.2</td>
<td>The number of patients in Population 4/4a and Population 5 should be marked as confidential as these data are not intended to be published. The above updates should also be made to the CS, where applicable.</td>
<td>Please highlight the population sample sizes as follows:
<table>
<tr><th colspan="2">Population 1</th><th colspan="2">Population 4 (abemaciclib+ET eligible)</th><th colspan="2">Population 5 (abemaciclib+ET ineligible)</th></tr>
<tr><td>Ribociclib+AI (n=2549)</td><td>AI (n=2552)</td><td>Ribociclib+AI (n=[redacted])</td><td>Ribociclib+AI (n=[redacted])</td><td>AI (n=[redacted])</td><td>Ribociclib+AI (n=[redacted])</td></tr>
</table>
</td>
<td>Text amended as suggested.</td>
</tr>
<tr>
<td>Page 53, Section 3.4.6</td>
<td>The directionality of MAIC results do not need to be marked as confidential, as per the approach in</td>
<td>“Compared with abemaciclib+ET, both prior to and after matching, ribociclib+AI was associated with statistically significantly reduced odds of Grade ≥3 diarrhoea, leukopenia, and lymphopenia, and statistically significantly increased odds of Grade ≥3 increased ALT and neutropenia.”</td>
<td>Text amended as suggested.</td>
</tr>
</table>

	the CS (Page 105).		
Page 56, Section 3.4.7	The directionality of both the MAIC results and the STC results do not need to be marked as confidential.	**"Ribociclib+AI versus abemaciclib+ET** The EAG considers that the company MAIC and STC methods were generally appropriate. The EAG notes that the OS STC results are statistically significant whereas the OS MAIC results are not statistically significant."	Text amended as suggested.
Page 58, Section 3.6.1	The number (%) of patients in the AI arm reporting hot flushes should be marked as confidential as these data are not intended to be published. The above update should also be made to the CS, where applicable.	In the AI arm, only arthralgia (1083/2441, 44.4%) and hot flushes ([redacted]	Text amended as suggested.
Page 60–61, Section 3.7.2	The statistical significance and direction of MAIC results do not need to be marked as confidential.	**"Ribociclib+AI versus abemaciclib+ET** The iDFS MAIC, iDFS STC and DRFS STC HR point estimate results are close to 1 and CIs include 1C. The OS MAIC HR results showed that, compared to abemaciclib+ET, ribociclib+AI numerically improved OS; only the OS STC result was statistically significant. Of all the ITC approaches considered by the company, the EAG considers that the STC approach was the most robust. The company has only generated STC results for the comparison of ribociclib+AI versus abemaciclib+ET (Population 4). This is a minor concern as Population 5 is the most representative of NHS patients who would be treated with ET and	Text amended as suggested.

		direct trial evidence for the comparison of ribociclib+AI versus AI is available from the NATALEE trial. The Grade ≥3 TEAE MAICs showed that compared with abemaciclib+ET, ribociclib+AI was associated with statistically significantly reduced odds of Grade ≥3 diarrhoea, leukopenia, and lymphopenia, and statistically significantly increased odds of Grade ≥3 increased ALT and neutropenia. **Ribociclib+AI versus ET** The iDFS and OS reweighted IPD analyses showed that, compared with ET, treatment with ribociclib+AI statistically significantly improved iDFS and numerically improved OS (CIs include 1). However, the EAG highlights that the AI arm of the NATALEE trial was used to inform the efficacy of ET in the reweighted IPD analyses."	
Table 48, Page 98, Section 8.1; Page 102, Section 8.2.1 (Appendix 2)	The number of patients in Population 4/4a should be marked as confidential as these data are not intended to be published. The above update should also be made to the CS, where applicable.	In Table 48 of the EAG report, the highlighting of the Summary of Company approach in the first row should be as follows: "The company conducted relevant population-adjusted MAICs and reweighted IPD analysis to compare the relative efficacy of ribociclib+AI vs abemaciclib+ET and vs ET (adjusted for potential confounding effects due to observed differences in baseline prognostic factors and effect modifiers) using IPD from the NATALEE trial (ribociclib+AI: n=[redacted] AI: n=[redacted]) and aggregate-level data from Cohort 1 of the monarchE trial12 (abemaciclib+ET: n=2555). Population 4 median follow-up was [redacted]months (April 2024 DCO). MonarchE trial12 median follow-up was 54.0 months (July 2023 DCO); these data were used to inform the company's MAICs and reweighted IPD analysis." On Page 102, Section 4.2.1 (Appendix 2) of the EAG report, the highlighting should be as follows: "The company's MAIC for TTE outcomes included patients receiving ribociclib+AI (n=[redacted]) and AI (n=[redacted]) from the NATALEE trial Population 4 as	Text amended as suggested.

<table>
<tr><td></td><td></td><td>well as patients receiving abemaciclib+ET (n=2,555) from the monarchE trial Cohort 1.”</td><td></td></tr>
<tr><td>Table 49, Page 104–106, Section 8.2.2 (Appendix 2)</td><td>The number of patients in Population 4/4a and Population 4b should be marked as confidential as these data are not intended to be published. The above updates should also be made to the CS, where applicable.</td><td>Please highlight the population sample sizes as follows:
<table>
<tr><th colspan="2">monarchE (Cohort 1)</th><th colspan="2">NATALEE-selected, unweighted (Population 4)</th><th colspan="2">NATALEE-selected, weighted (Population 4b)</th></tr>
<tr><td>Abemaciclib+ET (N=2,555)</td><td>ET (N=2,565)</td><td>Ribociclib+AI ([redacted])</td><td>AIa (N=[redacted])</td><td>Ribociclib+AI (ESS=[redacted])</td><td>AIa (ESS=[redacted])</td></tr>
</table></td><td>Text amended as suggested.</td></tr>
</table>

Company modelling inaccuracies

Location of incorrect marking in the model	Description of incorrect marking	Justification for amendment	EAG comment
Cells I11:I16 on the ‘Efficacy Waning’ tab in the CEM for all populations.	In the Company CQ and EAG base cases, the waning duration calculation in Cell H11 on the ‘Efficacy Waning’ tab of the CEM determines the waning duration in months by subtracting the cycle at which iDFS hazards are equal to the general population mortality, from the month waning is set to start. This results in a misalignment of time units (cycle versus month).	To ensure the CEM produces reliable deterministic results when the Company CQ and EAG base case settings are applied.	The model and the model revision instructions (EAR, Appendix 8.3) have been updated to

	The cell references in Cells I11:I16 on the 'Efficacy Waning' tab should be multiplied by the named range 'model.months.cycle' to convert the **cycle** at which iDFS hazards are equal to the general population mortality, to the **month** at which iDFS hazards are equal to the general population mortality, ensuring consistency in the time units used. For transparency, the column title in I10 on the 'Efficacy Waning' tab should be adjusted to 'Month at IDFS Hazards = Gen. Pop. Mort'.		reflect these comments.
Cells Y16:Y12 on the 'Comp2.Calc' tab in the CEM for all populations.	In the Company CQ and EAG base cases, the calculation of the weighted average HR to apply to the base case iDFS extrapolation for the ET alone arm to account for the poorer efficacy associated with tamoxifen was incorrect. The weighted HR incorrectly accounted for the proportion of patients receiving zoledronic acid, when this is concomitant treatment and therefore does not influence the weighting of the individual ET included in the basket. The formulae in Cells Y6:Y12 on the 'Comp2.Calc' tab should be updated to: =IF(OR(W6="",W6="Goserelin", **W6="Zoledronic acid"**),"",X6) With the appropriate cell references for each relevant row included in the formulae. This will remove zoledronic acid from the calculations used for the weighted HR.	To ensure the CEM produces reliable deterministic results when the Company CQ and EAG base case settings are applied.	The model and the model revision instructions (EAR, Appendix 8.3) have been updated to reflect these comments.