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:

1. **Comments on the Draft Guidance from Novartis**

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Breast Cancer Now
   b. Eli Lilly & Company

3. **Comments on the Draft Guidance from experts:**
   a. Mr Michal Sladkowski – clinical expert, nominated by the British Oncology Pharmacy Association

4. **Comments on the Draft Guidance received through the NICE website** (*Some comments have been redacted because NICE considered them to be inappropriate for publication)*

5. **External Assessment Group critique of company comments on the Draft Guidance**

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

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Novartis Pharmaceuticals UK Ltd
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state:	N/A

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• the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	1) Since April 2005, Novartis has exclusively licensed glycopyrronium bromide and certain intellectual property relating to its use and formulation from Vectura and its co-development partner, Sosei Heptares. The following inhaled medications are comprised of, or contain, glycopyrronium bromide: • Seebri® Breezhaler® (glycopyrronium bromide), used as a maintenance treatment for Chronic Obstructive Pulmonary Disease (COPD) o Ultibro® Breezhaler® (indacaterol/glycopyrronium bromide), used as a maintenance treatment for COPD • Enerzair® Breezhaler® (indacaterol/glycopyrronium bromide/mometasone furoate), used as a maintenance treatment for asthma uncontrolled with long-acting beta-agonist (LABA)/inhaled corticosteroid (ICS). Phillip Morris International (a tobacco company) acquired Vectura Group Limited (formerly Vectura Group plc). In Sep. 17, 2024– Vectura Fertin Pharma, Inc., an affiliate of Philip Morris International Inc. announced the sale of its subsidiary Vectura Group Ltd. (Vectura) to Molex Asia Holdings Ltd. 2) Novartis has been granted with an exclusive license from Japan Tobacco Inc. (JT) under JT patents on a world-wide basis for commercial rights to trametinib (Mekinist®; TMT212). Trametinib is a kinase inhibitor indicated as a single agent or in combination with dabrafenib for the treatment of several oncology indications. In 2015, as part of its purchase of oncology products from GlaxoSmithKline, Novartis obtained the worldwide exclusive rights granted by JT to develop, manufacture, and commercialise trametinib. JT retains co-promotion rights in Japan.
Name of commentator person completing form:	[redacted]

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Executive summary	The Company are encouraged by the positive recommendation for ribociclib plus aromatase inhibitor (AI) for the adjuvant treatment of patients with lymph-node positive, hormone receptor-positive (HR+), HER2-negative (HER2–) early breast cancer (EBC) that is present in:
	• at least 4 axillary lymph nodes, or
	• 1 to 3 axillary lymph nodes and the cancer:
	  ○ is Grade 3, defined as at least 8 points on the modified Bloom–Richardson grading system or equivalent, or
	  ○ has a primary tumour size of at least 5 cm.
	
	The introduction of ribociclib plus AI among this population (who represent patients with HR+/HER2– EBC for whom abemaciclib plus endocrine therapy [ET] is available; hereinafter referred to as Population 4 [node-positive high-risk eligible for abemaciclib] as per the Company submission) will provide an alternative, well-tolerated treatment option that has the potential to provide prolonged protection from breast cancer recurrence or progression into incurable advanced or metastatic disease.
	
	Whilst the Company are disappointed that ribociclib plus AI is not recommended for use within NHS England for the full population of patients with HR+/HER2– EBC at high risk of recurrence (the indication under review) in line with the MHRA license, we welcome the opportunity to participate in the consultation for this guidance. As part of this draft guidance document (DGD) response, the Company have provided the requested additional analyses, including a further cost-effectiveness analysis to support a positive recommendation for ribociclib plus AI among patients for whom treatment with abemaciclib plus ET is not an option (hereinafter referred to as Population 5 [NATALEE high-risk ineligible for abemaciclib], as per the Company submission). This patient population faces a substantial unmet need, with high recurrence rates and current treatment options limited to ET alone.
	
	The Company acknowledge the uncertainties that have been raised by the Committee regarding the evidence for Population 5 (NATALEE high-risk ineligible for abemaciclib). The Company also acknowledge that the Committee has identified ribociclib plus AI for Population 5 (NATALEE high-risk ineligible for abemaciclib) as a candidate for the Cancer Drugs Fund (CDF); the Company have since submitted a CDF proposal to overcome the uncertainty that the Committee have identified relating to data immaturity. In addition, where appropriate, additional evidence is provided in this DGD response to address and mitigate any other areas of uncertainty raised by the Committee.
	
	The methodology adopted for the cost-effectiveness analysis in Population 5 (NATALEE high-risk ineligible for abemaciclib) and subsequent results are provided in the following section and Appendices. The cost-effectiveness analysis demonstrates that, in both the Company's base case analysis and the scenario analyses adopting the Committee-preferred assumptions, ribociclib plus AI represents a cost-effective use of UK NHS resources vs ET in Population 5 (NATALEE high-risk ineligible for abemaciclib) at a £30,000 willingness-to-pay (WTP) threshold.

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1	**Cost-effectiveness analysis of ribociclib plus AI vs ET in Population 5 (NATALEE high-risk ineligible for abemaciclib)** In response to the DGD, the Company have conducted the requested cost-effectiveness analysis of ribociclib plus AI vs ET in Population 5 (NATALEE high-risk ineligible for abemaciclib). ***Population 5 definition*** Population 5 (NATALEE high-risk ineligible for abemaciclib) reflects all patients within the NATALEE ITT population (Population 1 [NATALEE ITT]) who would be ineligible for abemaciclib plus ET in UK NHS clinical practice. It therefore comprises patients in Population 1 (NATALEE ITT) but excluding those in Population 4 (node-positive high-risk eligible for abemaciclib [population evaluated in TA810]).[1] This population reflects a clinically important group of patients whose only treatment option within UK NHS clinical practice is ET. Clinical efficacy data (for invasive disease-free survival [iDFS]) for patients in Population 5 of the NATALEE trial are presented in Appendix A for completeness and demonstrate a statistically significant improvement in iDFS for patients treated with ribociclib plus AI versus AI (hazard ratio [HR]: [redacted]). ***Cost-effectiveness analysis overview*** The cost-effectiveness analysis of ribociclib plus AI vs ET in Population 5 (NATALEE high-risk ineligible for abemaciclib) has been conducted in line with the Company approach to the cost-effectiveness analysis for Population 1 (NATALEE intention-to-treat [ITT]) in the original Company submission, other than where data derived directly from Population 5 (NATALEE high risk ineligible for abemaciclib) are available and have been used, or where the Company base case analysis has been updated to align to the Committee-preferred assumptions for Population 4 (node-positive high-risk eligible for abemaciclib) outlined in the DGD – the population for which NICE have now recommended ribociclib plus AI as a treatment option in UK NHS clinical practice. Full details of the assumptions and inputs specific to Population 5 (NATALEE high risk ineligible for abemaciclib) that have been used for this cost-effectiveness analysis are provided in Appendix B. ***Summary of key base case assumptions*** The Company have applied the following Committee-preferred assumptions to the Company base case cost-effectiveness analysis in Population 5 (NATALEE high-risk ineligible for abemaciclib): • Cyclin dependent kinase (CDK) 4/6 inhibitor (i.e. ribociclib) treatment effect is based on the treatment waning duration applied previously in the Population 4 (node-positive high-risk eligible for abemaciclib) analysis

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	• iDFS event distributions for ET are equal to ribociclib plus AI – note that this has been updated to reflect the pooled iDFS event distribution across both arms of the NATALEE trial (ITT population)
	• ET-sensitive progression-free utility values are set equal to non-metastatic recurrence (NMR) utility values
	• The proportion of patients estimated to receive retreatment with CDK4/6 inhibitor therapy is 90% for the ET-sensitive distant recurrence (DR) substate (and 0% for the ET-resistant CDK4/6 inhibitor-resistant DR substate)
	• Adverse events (Grade ≥3) are graded according to severity
	
	The Committee-preferred assumptions that have not been incorporated into the Company base case cost-effectiveness analysis in Population 5 (NATALEE high risk ineligible for abemaciclib) are:
	
	• The Committee-preferred proportion of patients estimated to receive retreatment with CDK4/6 inhibitor therapy was 90% for the ET-resistant CDK4/6 inhibitor-sensitive DR substate
	  ○ The Committee-preferred proportion of CDK4/6 inhibitor retreatment (90%) is not reflective of UK NHS clinical practice; based on feedback received from 11 UK clinical experts, the Company base case adopts a retreatment proportion of 60% for the ET-resistant CDK4/6 inhibitor-sensitive DR substate
	• The Committee preferred to use the exponential curve for progression-free survival (PFS) and the Gamma curve for overall survival (OS) in the ET-sensitive DR substate, and the exponential curve for PFS and the Weibull (R) curve for OS in the ET-resistant DR substate
	  ○ The Company do not consider the Committee-preferred PFS and OS curves in the DR health states to be the most clinically plausible and therefore the Company base case aligns with the ingoing submission whereby the log-logistic (R) and lognormal (R) curves are utilised for OS and PFS, respectively, in the ET-resistant DR substate and the log-logistic and lognormal curves are utilised for OS and PFS, respectively, in the ET-sensitive DR substate
	
	For the above two assumptions (where the Company base case approach deviates from the Committee-preferred assumptions), additional evidence is presented in Appendix B to further support the Company's base case approach and reduce any remaining uncertainty around these assumptions. For completeness, the impact of adopting the Committee's preferred assumptions are shown in scenario analyses.
	
	As requested by the Committee in the DGD, the Company have also provided additional treatment waning scenarios and further analyses exploring alternative iDFS extrapolations in Population 5 (NATALEE high-risk ineligible for abemaciclib); details of these additional scenario analyses are presented in Appendix B, with results presented in Appendix C.
	
	Full details of the assumptions and inputs specific to Population 5 (NATALEE high-risk

ineligible for abemaciclib), and results from the cost-effectiveness analysis of ribociclib plus AI vs ET in Population 5 (NATALEE high-risk ineligible for abemaciclib) are presented in Appendix B, and Appendix C, respectively. A summary of the cost-effectiveness results is presented below.

Cost-effectiveness results

The results of the deterministic cost-effectiveness analysis in Population 5 (NATALEE high-risk ineligible for abemaciclib) demonstrate that ribociclib plus AI (with the patient access scheme [PAS] for ribociclib) is associated with [redacted] more quality-adjusted life years (QALYs) and increased total costs of [redacted] vs ET, resulting in an ICER of £15,459/QALY gained (Table 1). NHB results at both a £20,000 and £30,000 WTP threshold are positive, indicating ribociclib plus AI represents a cost-effective use of UK NHS resources vs ET in Population 5 (NATALEE high-risk ineligible for abemaciclib).

Probabilistic base case results are in line with the deterministic base case results, further supporting the conclusion that ribociclib plus AI represents a cost-effective use of NHS resources vs ET in Population 5 (NATALEE high-risk ineligible for abemaciclib; Table 2). Of note, ribociclib plus AI had a [redacted] and [redacted] probability of being cost-effective at WTP thresholds of £20,000 and £30,000/QALY gained, respectively (Figure 1).

Scenario analysis results are presented in Appendix C, Table 13 and demonstrate that, across all scenarios, ribociclib plus AI remains a cost-effective use of NHS resources at a WTP threshold of £30,000/QALY gained. Notably, across the majority of scenario analyses, the resulting ICER is less than £20,000/QALY gained.

Table 1: Deterministic analysis results: ribociclib plus AI vs ET – Population 5 (NATALEE high-risk ineligible for abemaciclib)

	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ET	[redacted]	15.733	[redacted]				
Ribociclib plus AI	[redacted]	16.421	[redacted]	[redacted]	0.647	[redacted]	15,459

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.

Table 2: Probabilistic analysis results: ribociclib plus AI vs ET – Population 5 (NATALEE high-risk ineligible for abemaciclib)

	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ET	[redacted]	15.857	[redacted]				
Ribociclib plus AI	[redacted]	16.467	[redacted]	[redacted]	0.610	[redacted]	16,116

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; ICER: incremental cost-effectiveness ratio;

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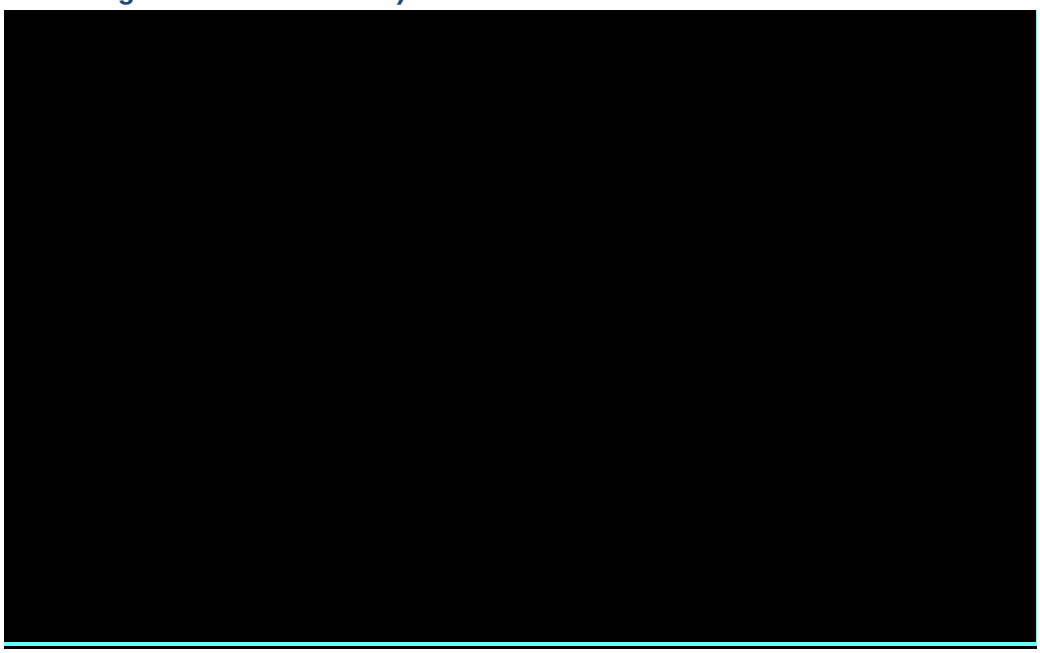
	Incr: incremental; LYG: life years gained; NHB: net health benefit; QALYs: quality-adjusted life years. **Figure 1: PSA scatter plot for ribociclib plus AI vs ET – Population 5 (NATALEE high-risk ineligible for abemaciclib)**  **Abbreviations**: AI: aromatase inhibitors; ET: endocrine therapy; ICER: incremental cost-effectiveness ratio; ITT: intention to treat; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years; WTP: willingness to pay.

Checklist for submitting comments

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- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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Appendix A Clinical effectiveness evidence for Population 5 (NATALEE high-risk ineligible for abemaciclib)

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 3, and the corresponding Kaplan-Meier curve is presented in Figure 2. At the April 2024 data cut, 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=[redacted]). 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 was [redacted]% (HR: [redacted]; one-sided stratified log-rank test p-value=[redacted]).

Table 3: Summary of iDFS in Population 5 (NATALEE high-risk ineligible for abemaciclib [April 2024 data cut]) from NATALEE

	Ribociclib plus AI (N=[redacted])	AI (N=[redacted])
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]

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Figure 2: Kaplan-Meier plot for iDFS 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; iDFS: invasive disease-free survival; ET: endocrine therapy; HR: hazard ratio.
Source: Novartis Data on File (2024).[2]

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Appendix B Methodology for the cost-effectiveness analysis for ribociclib plus AI vs ET in Population 5 (NATALEE high-risk ineligible for abemaciclib)

The approach to the cost-effectiveness analysis of ribociclib plus AI vs ET in Population 5 (NATALEE high-risk ineligible for abemaciclib) aligns with the Company cost-effectiveness analysis in Population 1 (NATALEE ITT), other than where data derived directly from Population 5 of the NATALEE trial have been applied, or where the Company base case has been updated to align with the Committee-preferred assumptions for Population 4 (node-positive high-risk eligible for abemaciclib) outlined in the DGD.

This section details any model inputs and assumptions specific to Population 5 that have been used for this cost-effectiveness analysis. All inputs and assumptions not detailed below remain in line with the Company's inputs and assumptions for Population 1 (NATALEE ITT), as previously presented in the original Company submission.

For the most part, the Company have updated the base case approach to align to the Committee's preferred assumptions detailed in the DGD. However, for two of the Committee's preferred assumptions, the Company maintain that the Company base case approach is most appropriate and have provided additional evidence in the sections below to support this and to reduce any remaining uncertainty surrounding the modelled inputs. Table 4 provides an overview of the approach taken for each of the Committee's preferred assumptions.

Table 4: Overview of the Company's approach to each of the Committee-preferred assumptions detailed in the DGD

Committee-preferred assumption	Company approach for the cost-effectiveness analysis of ribociclib plus AI vs AI in Population 5
CDK4/6 inhibitor treatment effect is maintained for 8 years and treatment waning lasts until the point at which iDFS reaches general population mortality	The Committee-preferred approach is applied in the base case analysis. The Committee-preferred approach to modelling treatment waning in Population 4 (node-positive high-risk eligible for abemaciclib) equates to waning starting at 8 years and continuing for [redacted] years. As such, the same approach has been applied to the base case analysis in Population 5 (NATALEE high-risk ineligible for abemaciclib). As per the Committee's request, additional treatment waning scenarios have been explored within scenario analyses.
iDFS event distributions for ET are equal to ribociclib plus an AI	The Committee-preferred approach is applied in the base case analysis. The Company have used pooled iDFS event distributions from the two treatment arms of the NATALEE trial (ITT population) to inform the iDFS event distributions for ribociclib plus AI and ET. As such, iDFS event distributions are equal for both treatments.
Exponential PFS and Gamma OS curves are used in ET-sensitive DR, and exponential PFS and Weibull (R) OS curves are used in ET-resistant DR sub-states	The Committee-preferred approach (use of the exponential PFS and Gamma OS curves in ET-sensitive DR substate, and the exponential PFS and Weibull [R] OS curves in ET-resistant DR substate) is not applied in the base case analysis. Instead, the Company base case approach to modelling long-term OS and PFS for Population 1 (NATALEE ITT) in the DR health state has been applied, whereby the curves for PFS and OS used as part of the ingoing Company submission are utilised: lognormal PFS and log-logistic OS curves in the ET-sensitive DR substate, and the lognormal (R) PFS and log-logistic (R) OS curves in ET-resistant DR substate. Additional supportive evidence is presented to justify the use of the Company curve choices in the DR health state (see Appendix B.4).

	Scenario analyses have been conducted whereby different extrapolations are explored for OS and PFS in both the ET-resistant and ET-sensitive DR substates.
The proportion of people having retreatment with CDK4/6 inhibitor therapy is 90% for both ET-sensitive and ET-resistant DR substates	ET-sensitive DR substate: The Committee-preferred approach is applied in the base case analysis.
	ET-resistant CDK4/6 inhibitor-resistant DR substate: The Committee-preferred approach is applied in the base case analysis.
	ET-resistant CDK4/6 inhibitor-sensitive DR substate: The Committee-preferred approach is not applied in the base case analysis. Instead, the Company base case models 60% of patients to be retreated with a CDK4/6 inhibitor in the ET-resistant CDK4/6 inhibitor-sensitive DR substate, based on an additional clinical validation exercise conducted by the Company in April–May 2025 (see Appendix B.7). Scenario analyses have been conducted whereby different treatment mixes are used in the ET-resistant CDK4/6 inhibitor-sensitive DR substate.
ET-sensitive progression-free utility values equal NMR utility values	The Committee-preferred approach is applied in the base case analysis.
Adverse events (Grade ≥3) are graded according to severity	The Committee-preferred approach is applied in the base case analysis.

Abbreviations: AI: aromatase inhibitor; CDK: cyclin-dependent kinase; DR: distant recurrence; ET: endocrine therapy; iDFS: invasive disease-free survival; ITT: intention-to-treat; OS: overall survival; PFS: progression-free survival;

Lastly, in response to the Committee's request that the Company provide more evidence exploring alternative iDFS extrapolations, the Company have conducted several new scenario analyses using different curve choices to estimate long-term iDFS in Population 5 (NATALEE high-risk ineligible for abemaciclib).

Appendix B.1 Modelled baseline characteristics

Baseline characteristics informing the cost-effectiveness analysis between ribociclib plus AI and ET in Population 5 (NATALEE high-risk ineligible for abemaciclib) are aligned to the baseline characteristics of Population 5 in the NATALEE trial (Table 5).

Table 5: Summary of baseline characteristics used in the cost-effectiveness analyses

Variable	Population 5 (NATALEE high-risk ineligible for abemaciclib)
Mean age (years)	[redacted]
Proportion Female	[redacted]
Mean BSA (m^2)	[redacted]
Mean weight (Kg)	[redacted]

Abbreviations: BSA: body surface area.

Appendix B.2 iDFS event distributions

The iDFS event distributions informing the cost-effectiveness analysis in Population 5 (NATALEE high-risk ineligible for abemaciclib) are derived from the ITT population of the NATALEE trial (April 2024 data cut).[3] In line with the Committee-preferred assumptions, iDFS event distributions for ET are equal to the iDFS event distributions for ribociclib plus AI (i.e., the iDFS event distributions are equal for the intervention and comparator). Specifically, the Population 1 (NATALEE ITT) iDFS event distributions in the AI arm and the

ribociclib plus AI arm of the NATALEE trial (ITT population) have been pooled across the two treatments, with the pooled iDFS event distributions subsequently informing the cost-effectiveness analysis in Population 5 (NATALEE high-risk ineligible for abemaciclib).

Table 6 presents the pooled Population 1 (NATALEE ITT) iDFS event distributions informing the base case cost-effectiveness analysis of ribociclib plus AI vs AI in Population 5 (NATALEE high-risk ineligible for abemaciclib).

Table 6: Proportion of iDFS events that are SPM, NMR, DR or death in Population 1 (NATALEE ITT)

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})
Ribociclib plus AI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	[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).[3]

Appendix B.3 Parametric survival distributions – recurrence-free health states

iDFS

Probabilities of iDFS events for patients receiving ribociclib plus AI and ET for Population 5 (NATALEE high-risk ineligible for abemaciclib) were based on data from Population 5 of the NATALEE trial (April 2024 data cut).[3]

Long-term distributions used in the cost-effectiveness analysis of ribociclib plus AI vs ET in Population 5 (NATALEE high-risk ineligible for abemaciclib) were selected following the guidance set out in NICE DSU TSD 14.[4]

The restricted mean survival time (RMST) by treatment group for Population 5 (NATALEE high-risk ineligible for abemaciclib) is shown in Figure 3.

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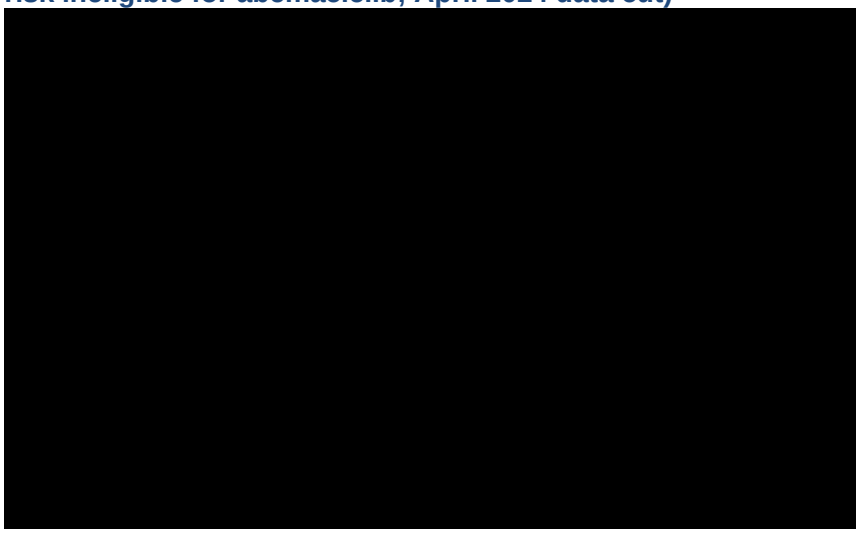
Figure 3: Restricted mean survival time plots for iDFS in Population 5 (NATALEE high-risk ineligible for abemaciclib; April 2024 data cut), by randomised treatment arms

Footnotes: The AI arm of the NATALEE trial is termed ET in the above figure and was used to inform the efficacy of ET as a comparator.
Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; iDFS: invasive disease-free survival.

A plot of a smoothed curve fit to Schoenfeld residuals for iDFS of Population 5 (NATALEE high-risk ineligible for abemaciclib) is shown in Figure 4. The curve is [redacted].

Figure 4: Plot of smoothed curve fit to Schoenfeld residuals for iDFS in Population 5 (NATALEE high-risk ineligible for abemaciclib; April 2024 data cut)



Abbreviations: HR: hazard ratio; iDFS: invasive disease-free survival.

A ranking of parametric distributions fit to iDFS by the fit statistics are shown in Table 7.

Table 7: Fit statistics for parametric distributions fit to iDFS for Population 5 (NATALEE high-risk ineligible for abemaciclib; April 2024 data cut)

Distribution	AIC	AICc	BIC
Exponential	1,947.50	1,947.50	1,958.50

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Distribution	AIC	AICc	BIC
Gamma (R)	1,944.90	1,944.90	1,961.30
Log-Logistic (R)	1,944.80	1,944.80	1,961.30
Weibull (R)	1,945.00	1,945.00	1,961.40
Lognormal (R)	1,945.60	1,945.60	1,962.10
Gompertz (R)	1,947.20	1,947.20	1,963.60
RCS Weibull (R)	1,946.10	1,946.10	1,968.10
RCS Log-Logistic (R)	1,946.20	1,946.20	1,968.20
Gen. Gamma (R)	1,946.50	1,946.50	1,968.50
Log-Logistic (U)	1,946.60	1,946.60	1,968.50
Gamma (U)	1,946.60	1,946.70	1,968.60
Weibull (U)	1,946.70	1,946.80	1,968.70
Lognormal (U)	1,946.90	1,947.00	1,968.90
Gompertz (U)	1,948.60	1,948.60	1,970.60
Gen. F (R)	1,948.50	1,948.50	1,976.00
RCS Weibull (U)	1,949.40	1,949.40	1,982.30
RCS Log-Logistic (U)	1,949.40	1,949.50	1,982.40
Gen. Gamma (U)	1,949.90	1,950.00	1,982.90
Gen. F (U)	1,953.90	1,954.00	1,997.90

Footnotes: A smaller fit statistic is better.
Abbreviation: AIC: Akaike information criterion; AICc: corrected Akaike information criterion; BIC: Bayesian information criterion; iDFS: invasive disease-free survival; R: restricted; RCS: restricted cubic splines; U: unrestricted.

Long-term projections of iDFS (out to 20 years) for the top six best statistically fitting distributions are shown in Figure 5.

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Figure 5: Long-term projections of iDFS based on parametric survival distributions fit to iDFS for Population 5 (NATALEE high-risk ineligible for abemaciclib; April 2024 data cut), by randomised treatment arms

Footnotes: The 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 is termed ET in the above figure and was used to inform the efficacy of ET as a comparator.
Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; iDFS: invasive disease-free survival; RCS: restricted cubic splines.

Lacking data on long-term iDFS for a population consistent with the NATALEE trial, iDFS curve selection was based on statistical goodness-of-fit, visual fit, and assessment of the clinical plausibility of long-term extrapolations. The Company identified a published retrospective real-world data study which reports iDFS for patients with HR+ HER2- EBC that received ET. The 10-year iDFS for patients with stage II EBC (which is a similar population to Population 5 [NATALEE high-risk ineligible for abemaciclib]) is reported as 59.5%, while median time to an iDFS event was 160.2 months which suggests that the Lognormal (R) is not clinically plausible.[5] The 20-year iDFS for the Gompertz (R) is ~80% which is unlikely to be clinically plausible. The remaining extrapolations have similar 10- and 20-year iDFS. The Gamma (R) distribution had the second-best fit based on BIC and excellent visual fit to the Kaplan-Meier iDFS for both arms in NATALEE. The Gamma (R) distribution had estimated difference in RMST of [redacted] months, which was close to the median of [redacted] months across all fitted distributions. As such, the Gamma (R) model was used in the base case.

Following the Committee's additional request for more scenario analyses exploring alternative iDFS extrapolations, the Company have conducted eight new scenario analyses using different parametric distributions to estimate long-term iDFS among Population 5 (NATALEE high-risk ineligible for abemaciclib). Specifically, all restricted extrapolations are explored in scenario analyses:

- Log-Logistic (R)
- Weibull (R)

- Lognormal (R)
- Gompertz (R)
- RCS Weibull (R)
- RCS Log-Logistic (R)
- Gen. Gamma (R)
- Gen. F (R)

Figure 6 depicts the long-term (20-year) iDFS extrapolations for ET that are adopted in the base case and scenario analyses.

Figure 6: ET: Long-term iDFS extrapolations (base case and scenario analysis)

The results of the scenario analyses are presented in Appendix C, and demonstrate that across all scenario analyses adopting differing long-term extrapolations of iDFS, ribociclib plus AI remains a cost-effective use of NHS resources at a WTP threshold of £30,000/QALY gained. Of note, across the majority of curve choices, the resulting ICER is below £20,000/QALY gained.

Time to treatment discontinuation (TTD)

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Ribociclib

Given TTD data from NATALEE are mature, the probabilities of TTD events for patients receiving ribociclib in Population 5 (NATALEE high-risk ineligible for abemaciclib) are estimated using the Kaplan-Meier plot for TTD from Population 5 (NATALEE high-risk ineligible for abemaciclib) in NATALEE directly.

AI (in combination with ribociclib) and ET

Curve selection for TTD AI/ET is based on statistical goodness-of-fit, visual fit, a subjective assessment of the clinical plausibility of long-term extrapolations, and the assumption that treatment duration with AI would be no longer than 5 years in the model. The best fitting model based on BIC was the Weibull (R) distribution; this distribution is selected for TTD AI in the model.

Summary

A summary of the extrapolations for iDFS (base case and scenario analyses) and TTD for ribociclib plus AI vs ET in Population 5 (NATALEE high-risk ineligible for abemaciclib) is presented in Table 8.

Table 8: Summary of extrapolations for iDFS and TTD in Population 5 (NATALEE high-risk ineligible for abemaciclib)

Treatment arm	Base case extrapolation for iDFS	Scenario analysis extrapolations for iDFS	Base case extrapolation for TTD
Ribociclib plus AI	Gamma (R)	• Log-Logistic (R) • Weibull (R) • Lognormal (R) • Gompertz (R) • RCS Weibull (R) • RCS Log-Logistic (R) • Gen. Gamma (R) • Gen. F (R)	• Ribociclib: TTD Kaplan-Meier curve • AI: Weibull (R)
ET	Gamma (R)	• Log-Logistic (R) • Weibull (R) • Lognormal (R) • Gompertz (R) • RCS Weibull (R) • RCS Log-Logistic (R) • Gen. Gamma (R) • Gen. F (R)	• Weibull (R)

Abbreviations: AI: aromatase inhibitors; ET: endocrine therapy; iDFS: invasive disease-free survival; R: restricted; TTD: time-to-treatment discontinuation.

Appendix B.4 Parametric survival distributions – distant recurrence health state

The Company maintain that the Company's long-term estimations of OS and PFS for Population 1 (NATALEE ITT) in the ET-resistant and ET-sensitive DR substates are most appropriate and therefore in the base case cost-effectiveness analysis of ribociclib plus AI vs ET in Population 5 (NATALEE high-risk ineligible for abemaciclib), extrapolations of OS and PFS in the ET-resistant and ET-sensitive DR substates align to those used in the Company submission for Population 1 (NATALEE ITT; Table 9).

However, the Company acknowledge the Committee's concerns that the Company's [and EAG's] long-term

estimates of PFS and OS are subject to uncertainty because of a lack of long-term data, and that, as stated in the NICE DGD, clinical experts "could not determine which curves are more appropriate". As such, the Company have since conducted a pragmatic search of the literature to identify any further published long-term outcome data for CDK4/6 inhibitors that could be used validate the OS and PFS curves for the ET-sensitive and ET-resistant DR substates. The pragmatic literature search identified a recently published retrospective real-world data study by Rugo *et al.* (2025) that analysed long-term OS outcomes for adults (N=9,146) with HR+/HER2– advanced or metastatic breast cancer who received a CDK4/6 inhibitor plus AI in the first-line (metastatic) treatment setting.[6] With a follow up of >100 months, this study was used to validate the ET-sensitive OS curves informing the cost-effectiveness analysis in Population 5 (NATALEE high-risk ineligible for abemaciclib).

Rugo *et al.* (2025) identified OS rates of ~30% at 9 years post-treatment with a CDK4/6 inhibitor (palbociclib) plus AI in the first-line (metastatic) treatment setting.[6] These real-world findings from a large sample of patients with HR+/HER2– advanced or metastatic breast cancer are higher than both the Company- and Committee-preferred curves, which estimate OS to be ~25% and ~20% at 10 years, respectively, in the ET-sensitive DR substate. As such, while both the Company- and Committee-preferred curves may represent conservative estimates of long-term OS outcomes in the ET-sensitive DR disease setting, the study by Rugo *et al.* (2025) indicates that the Company's curves are closer to outcomes observed in clinical practice. Therefore the Company maintain that the log-logistic extrapolation is the most appropriate curve to adopt to model OS in the ET-sensitive DR substate.

Of note, the Company were not able to identify any published studies providing long-term estimates for PFS in the ET-sensitive substate, nor any published studies providing long-term estimates for OS or PFS in the ET-resistant substate.

Scenario analyses

For completeness, the Company have conducted additional scenario analyses to explore the impact of using alternative extrapolations for OS and PFS in the ET-resistant and ET-sensitive DR substates. These scenario analyses consider the Committee-preferred extrapolations which are considered to be the most conservative, as well as an alternative set of extrapolations which predict long-term PFS and OS to fall between that predicted by the Company base case and the Committee's preferred choices. Of note, for OS in the ET-sensitive health state and PFS in the ET-resistant health state, no standard curves fell between the Company's and Committee's preferred curve choices; as such, in these cases, new curves have been derived by calculating the average of the Company's and Committee's preferred curves.

See Table 9 for a summary of the extrapolations used for OS and PFS in the ET-resistant and ET-sensitive DR health states. Figure 7 depicts the three different curve choices explored in the base case and two scenario analyses for PFS and OS, for both ET-resistant and ET-sensitive DR substate. The results of the scenario analyses are presented in Appendix C. Both scenario analyses demonstrate that ribociclib plus AI remains a cost-effective use of NHS resources at a WTP threshold of £20,000/QALY gained.

Table 9: Summary of extrapolations for OS and PFS in the DR health states

	Treatment arm	Base case extrapolation for OS	Scenario analysis extrapolations for OS	Base case extrapolation for PFS	Scenario analysis extrapolations for PFS

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ET-sensitive	Ribociclib plus AI	Log-logistic	• Average of log-logistic (Company-preferred) and Gamma (Committee-preferred) • Gamma	Lognormal	• GenGamma • Exponential
ET-resistant	Ribociclib plus fulvestrant	Loglogistic (R)	• RCS lognormal (U) • Weibull (R)	Lognormal (R)	• Average of lognormal (R) (Company-preferred) and exponential (Committee-preferred) • Exponential

Footnotes: No standard curves fell between the Company's and Committee's preferred curve choices; as such, in these cases, new curves have been derived by calculating the average of the Company's and Committee's preferred curves.
Abbreviations: AI: aromatase inhibitors; DR: distant recurrence; ET: endocrine therapy; OS: overall survival; PFS: progression-free survival.

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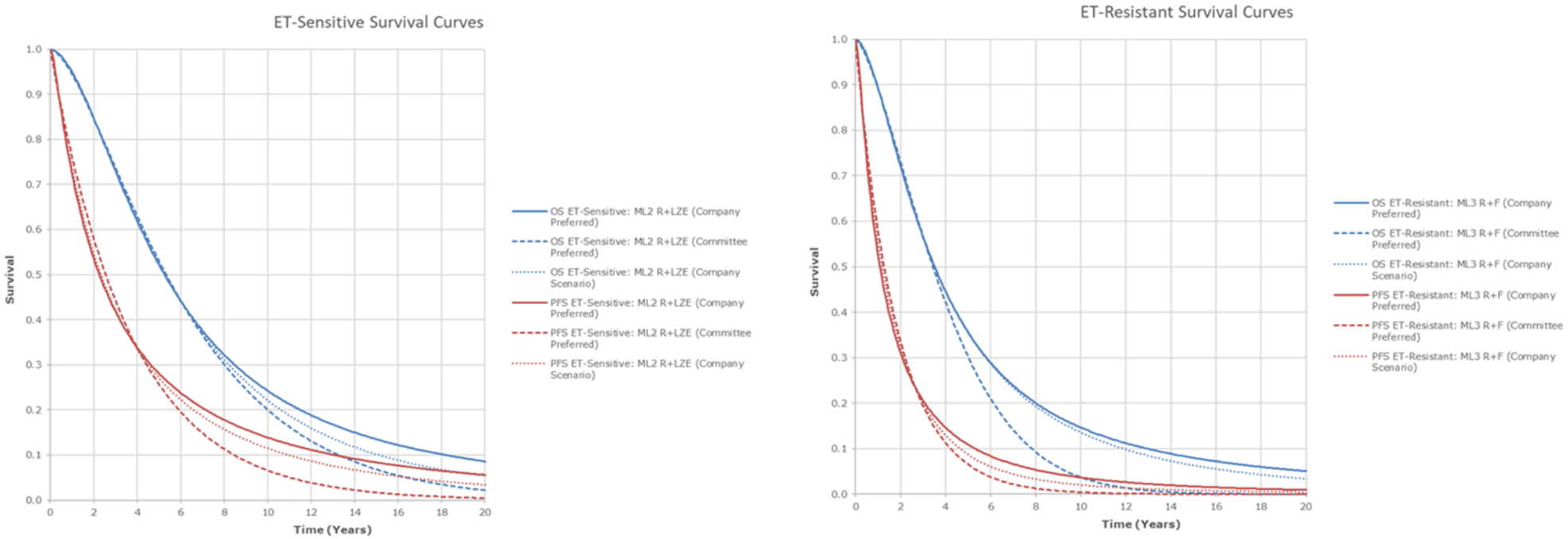
Figure 7: Extrapolations for OS and PFS in the DR health states



Abbreviations: F: fulvestrant; LZE: letrozole; R: ribociclib; OS: overall survival; PFS: progression-free survival.

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Appendix B.5 Treatment effect waning

In line with the Committee's preferred assumption on treatment effect waning for Population 4 (node-positive high-risk eligible for abemaciclib), in the cost-effectiveness analysis for Population 5 (NATALEE high-risk ineligible for abemaciclib) the treatment effect of ribociclib is assumed to be maintained for 8 years, after which the treatment effect is assumed to wane over time. Specifically, the Committee's preferred approach for Population 4 (node-positive high-risk eligible for abemaciclib) equates to treatment effect waning initiating at 8 years and continuing for a duration of [redacted] years; the base case cost-effectiveness analysis in Population 5 (NATALEE high-risk ineligible for abemaciclib) aligns directly with this approach.

Scenario analyses

in recognition of the Committee's additional requests, the Company have since conducted a wider range of treatment-waning scenarios, exploring the impact of reducing the period over which the treatment effect of ribociclib is waned. Specifically, the following six treatment waning scenario analyses have been conducted:

- Treatment effect assumed constant up to 8 years, followed by 17.5 years of treatment waning
- Treatment effect assumed constant up to 8 years, followed by 15 years of treatment waning
- Treatment effect assumed constant up to 8 years, followed by 12.5 years of treatment waning
- Treatment effect assumed constant up to 8 years, followed by 10 years of treatment waning
- Treatment effect assumed constant up to 8 years, followed by 7.5 years of treatment waning
- Treatment effect assumed constant up to 8 years, followed by 5 years of treatment waning

The results of the scenario analyses are presented in Appendix C; all scenario analyses exploring differing treatment effect waning durations demonstrate ribociclib plus AI to be a cost-effective use of NHS resources at a £30,000 WTP threshold. Of note, all scenario analyses where the treatment effect was assumed constant up to 8 years, followed by 10 or more years of treatment waning demonstrate ribociclib plus AI to be a cost-effective use of NHS resources at a £20,000 WTP threshold.

Appendix B.6 Adverse events

In line with the Company base case approach for Population 1 (NATALEE ITT), AEs considered in the model included all-cause Grade 3+ adverse events with an incidence ≥5% for any of the comparators of interest. For the cost-effectiveness analysis in Population 5 (NATALEE high-risk ineligible for abemaciclib), 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 population (i.e., Population 5; April 2024 data cut; see Table 10).[3]

Table 10: Grade 3+ adverse events from the NATALEE trial included in the cost-effectiveness analysis in Population 5 (NATALEE high-risk ineligible for abemaciclib)

Adverse event	Ribociclib plus AI	ET[a]
Alanine aminotransferase increased	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]

Footnotes: [a]The AI arm of the NATALEE trial was used to inform the efficacy of ET.
Abbreviations: AI: aromatase inhibitor; ET: endocrine therapy.
Source: Novartis Data on File (NATALEE Clinical Study Report April 2024 Data Cut: Table 4-6).[3]

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Appendix B.7 Treatment mixes in DR health state

DR health state (ET-resistant and ET-sensitive)

Treatment mixes in the ET-sensitive DR health state and the ET-resistant CDK4/6 inhibitor-resistant substates are modelled in line with the Committee's preferred assumptions (Table 12). Specifically, for the ET-sensitive substate, 90% of patients are assumed to receive retreatment with a CDK4/6 inhibitor (in line with clinical expert feedback to the Company). For the ET-resistant CDK4/6 inhibitor-resistant substate, it is assumed that no patients will receive retreatment with a CDK4/6 inhibitor.

For the ET-resistant CDK4/6 inhibitor-sensitive substate, the Company acknowledge that there is uncertainty associated with the proportion of patients receiving retreatment with a CDK4/6 inhibitor in the advanced or metastatic breast cancer setting, and has therefore conducted a further clinical validation exercise to inform the Company's base case approach to modelling treatment mixes in this substate. Specifically, a clinical validation exercise was conducted across April and May 2025 and involved 11 UK-based clinical experts; the individual results from this exercise are presented in Table 11.

Table 11: Individual results from the additional clinical validation exercise conducted by the Company in April–May 2025

Clinical Expert	Would you consider retreatment with a CDK4/6 inhibitor?	Estimated proportion of patients you would rechallenge with a CDK4/6 inhibitor?
1	Potentially	No estimate given
2	Yes	No estimate given
3	Yes	50%
4	Yes	60%
5	Yes	60-70%
6	Yes	60-75%
7	Yes	Most
8	Yes	Most
9	Yes	Most
10	Yes	Same as ET monotherapy
11	Yes	Same as ET monotherapy

Abbreviations: CDK4/6: cyclin dependent kinase 4/6; ET: endocrine therapy.

Of note, the clinical experts highlighted that because adjuvant CDK4/6 inhibitors have only been available in UK clinical practice since 2022 (with the introduction of abemaciclib), they have not yet had patients who would be categorised as ET-resistant CDK4/6 inhibitor-sensitive patients. A number of clinical experts noted that there was no direct evidence to support the use of retreatment with a CDK4/6 inhibitor in the advanced or metastatic breast cancer setting following adjuvant CDK4/6 inhibitor use. Despite this, the majority of clinical experts (10 out of 11) indicated that they would consider retreatment with a CDK4/6 inhibitor among this population of patients. However, this would be determined on a case-by-case basis, taking into account various characteristics (such as endocrine sensitivity characteristics, location of metastasis, volume of relapse, presence of PIK3CA/AKT/PTEN alterations and visceral crisis status) before determining if the patient would be retreated with a CDK4/6 inhibitor. The majority of the clinical experts indicated that they would be less likely to retreat patients with a CDK4/6 inhibitor if they had experienced an early relapse,

compared to those who had a later relapse.

Among the clinical experts who provided an estimate for the proportion of patients that they would retreat with a CDK4/6 inhibitor, two experts stated that they would treat these patients the same as if they had ET monotherapy in the adjuvant setting, three experts stated that they would retreat most patients, while four experts estimated the proportion retreated with a CDK4/6 inhibitor to be between 50% and 75%. As such, the Committee's preferred assumption to model CDK4/6 inhibitor retreatment at 90% in the ET-resistant CDK4/6 inhibitor-sensitive substate is not considered reflective of UK NHS clinical practice. Therefore, in the base case cost-effectiveness analysis of ribociclib plus AI vs ET in Population 5 (NATALEE high-risk ineligible for abemaciclib), the Company have modelled the proportion of patients receiving retreatment with a CDK4/6 inhibitor in the ET-resistant CDK4/6 inhibitor-sensitive substate to be 60%, which better reflects UK clinical expert feedback (Table 12).

Table 12: Treatment mix: DR health state

DR substate	CDK eligibility	Treatment	Ribociclib plus AI
ET-resistant	Resistant	Ribociclib plus fulvestrant	[redacted]
		Palbociclib plus fulvestrant	[redacted]
		Abemaciclib plus fulvestrant	[redacted]
		Everolimus plus exemestane	[redacted]
		Capecitabine	[redacted]
		Paclitaxel	[redacted]
		Alpelisib	[redacted]
ET-resistant	Sensitive	Ribociclib plus fulvestrant	[redacted]
		Palbociclib plus fulvestrant	[redacted]
		Abemaciclib plus fulvestrant	[redacted]
		Everolimus plus exemestane	[redacted]
		Capecitabine	[redacted]
		Paclitaxel	[redacted]
		Alpelisib	[redacted]
ET-sensitive	Sensitive	Ribociclib plus NSAI	[redacted]
		Palbociclib plus NSAI	[redacted]
		Abemaciclib plus NSAI	[redacted]
		Capecitabine	[redacted]
		Letrozole	[redacted]
		Paclitaxel	[redacted]

Abbreviations: AI: aromatase inhibitor; CDK: cyclin-dependent kinase; DR: distant recurrence; ET: endocrine therapy; NSAI: non-steroidal aromatase inhibitor.

Scenario analyses

While the Company's adjusted base case approach is based on recent insights from 11 UK-based clinical experts, the Company acknowledge that there remains inherent uncertainty around the proportion of patients who would receive retreatment with a CDK4/6 inhibitor in clinical practice, given the recency of the NICE recommendation for abemaciclib in the adjuvant treatment setting. As such, to explore the impact of this

possible uncertainty on the cost-effectiveness results for Population 5 (NATALEE high-risk ineligible for abemaciclib), two further scenarios have been conducted whereby the proportion of patients receiving retreatment with a CDK4/6 inhibitor is modelled at 75% and at 90% (the Committee-preferred assumption), respectively. The results of the scenario analyses are presented in Appendix C; for both scenario analyses (with CDK4/6 inhibitor retreatment modelled at 75% and at 90%), ribociclib plus AI remains a cost-effective use of NHS resources at a £20,000 WTP threshold.

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Appendix C Cost-effectiveness results for ribociclib plus AI vs ET in Population 5 (NATALEE high-risk ineligible for abemaciclib)

Deterministic and probabilistic cost-effectiveness analysis results for ribociclib plus AI vs ET in Population 5 (NATALEE high-risk ineligible for abemaciclib) have been presented previously.

This section presents the cost-effectiveness acceptability curve (CEAC) for ribociclib plus AI vs ET in Population 5 (NATALEE high-risk ineligible for abemaciclib; Figure 8) and the results from the scenario analyses conducted in Population 5 (NATALEE high-risk ineligible for abemaciclib; Table 13).

Figure 8: CEAC for ribociclib plus AI vs ET – Population 5 (NATALEE high-risk ineligible for abemaciclib)

Abbreviations: AI: aromatase inhibitor; CEAC: cost-effectiveness acceptability curve; ET: endocrine therapy; QALY: quality-adjusted life year; ribo: ribociclib; WTP: willingness to pay.

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Table 13: Scenario analysis results – Population 5 (NATALEE high-risk ineligible 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]	**15,459**	0.106	**0.225**
iDFS extrapolation (ribociclib plus AI/ET)	Gamma (R)	Gen. F (R)	[redacted]	[redacted]	20,795	-0.015	0.119
		Gen. Gamma (R)	[redacted]	[redacted]	20,787	-0.015	0.119
		Gompertz (R)	[redacted]	[redacted]	17,824	0.053	0.196
		Log-logistic (R)	[redacted]	[redacted]	18,283	0.036	0.163
		Lognormal (R)	[redacted]	[redacted]	29,081	-0.141	0.010
		RCS Log-Logistic (R)	[redacted]	[redacted]	19,269	0.015	0.145
		RCS Weibull (R)	[redacted]	[redacted]	15,694	0.099	0.218
		Weibull (R)	[redacted]	[redacted]	14,553	0.132	0.249
Treatment waning	‘Carryover benefit’ of a constant treatment effect lasting up to 8 years, after which the treatment effect was modelled to wane over [redacted] years	Treatment effect assumed constant up to 8 years, followed by 17.5 years of treatment waning	[redacted]	[redacted]	15,926	0.094	0.216
		Treatment effect assumed constant up to 8 years, followed by 15 years of treatment waning	[redacted]	[redacted]	16,947	0.068	0.195
		Treatment effect assumed constant up to 8 years, followed by 12.5 years of treatment waning	[redacted]	[redacted]	18,241	0.038	0.170
		Treatment effect assumed constant up to 8 years, followed by 10 years of treatment waning	[redacted]	[redacted]	19,860	0.003	0.141
		Treatment effect assumed constant up to 8 years, followed by 7.5 years of treatment waning	[redacted]	[redacted]	21,855	-0.037	0.107

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Parameter	Base case	Scenario analysis	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
		Treatment effect assumed constant up to 8 years, followed by 5 years of treatment waning	[redacted]	[redacted]	24,535	-0.084	0.067
Efficacy of post-progression therapies in DR health state	ET-resistant MONALEESA-3 OS: Loglogistic (R) ET-sensitive MONALEESA-2 OS: Log-logistic ET-resistant MONALEESA-3 PFS: Lognormal (R) ET-sensitive MONALEESA-2 PFS: Lognormal	**Company scenario curves:** ET-resistant MONALEESA-3 OS: RCS lognormal (U) ET-sensitive MONALEESA-2 OS: Average of log-logistic (Company-preferred) and Gamma (Committee-preferred) ET-resistant MONALEESA-3 PFS: Average of lognormal (R) (Company-preferred) and exponential (Committee-preferred) ET-sensitive MONALEESA-2 PFS: GenGamma	[redacted]	[redacted]	16,442	0.086	0.218
		Committee-preferred curves: ET-resistant MONALEESA-3 OS: Weibull (R) ET-sensitive MONALEESA-2 OS: Gamma ET-resistant MONALEESA-3 PFS: Exponential ET-sensitive MONALEESA-2 PFS: Exponential	[redacted]	[redacted]	18,594	0.037	0.203
Treatment mix (DR health state)	60% of patients in the ribociclib plus AI arm of the model would receive	75% of the ribociclib plus AI arm of the model would receive retreatment with a CDK4/6 inhibitor in the ET-	[redacted]	[redacted]	16,542	0.081	0.210

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Parameter	Base case	Scenario analysis	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
	retreatment with a CDK4/6 inhibitor in the ET-resistant, CDK4/6 inhibitor sensitive DR health state	resistant, CDK4/6 sensitive inhibitor DR health state					
		90% of the ribociclib plus AI arm of the model would receive retreatment with a CDK4/6 inhibitor in the ET-resistant, CDK4/6 inhibitor sensitive DR health state	[redacted]	[redacted]	17,611	0.056	0.195

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5. O'Shaughnessy J, Tolaney SM, Yardley DA, et al. Real-world risk of recurrence and treatment outcomes with adjuvant endocrine therapy in patients with stage II-III HR+/HER2- early breast cancer. The Breast 2025;81:104437.
6. Rugo HS, Layman RM, Lynce F, et al. Comparative overall survival of CDK4/6 inhibitors plus an aromatase inhibitor in HR+/HER2- metastatic breast cancer in the US real-world setting. ESMO Open 2025;10:104103.

NICE 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]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Thursday 15 May 2025. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Breast Cancer Now

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NICE 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]

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are pleased that ribociclib with an aromatase inhibitor has been approved for use in the population of people with HR-positive, HER2-negative early breast cancer at high risk of

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	recurrence who already have access to abemaciclib. Additional treatment options provide greater choice for patients and clinicians, which we know is valued.
2	However, we are concerned that the current draft guidance will not allow those with node-negative disease at high risk of recurrence, or those with 1-3 positive nodes and no other high risk characteristics, to benefit from ribociclib. Patients in these groups do not currently have access to a CDK4/6 inhibitor to reduce the risk of their breast cancer returning. Ribociclib could have addressed this unmet need, helping to alleviate some of the anxiety associated with a risk of recurrence for these patients.
3	We hope that NICE are able to work closely with the company to resolve the uncertainties around cost-effectiveness, to ensure that the full licensed population is able to access ribociclib.
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Insert extra rows as needed

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Eli Lilly and Company Limited

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	In regards to inaccuracies, Lilly wish to raise one point, please can NICE review the wording on page 10, section 3.5, and page 24, section 3.24, when describing population 4 (where abemaciclib is an option). It currently states: *"The committee noted that population 4 represented a population of people with cancer for which abemaciclib plus endocrine treatment is an option, as outlined in NICE Technology Appraisal*

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	Guidance TA810. That is, lymph-node positive with at least 4 axillary lymph nodes, or 1 to 3 axillary lymph nodes, and when there is grade 3 disease or a primary tumour size of at least 5 cm."
	
	Lilly asks that this is amended to the below (to be clear that this is in reference to positive axillary lymph nodes and the additional criteria only applies to those with 1-3 positive lymph nodes and could have either grade 3 or tumour size at least 5cm or both of these.
	That is, lymph-node positive with:
	• at least 4 positive axillary lymph nodes, or
	• 1 to 3 positive axillary lymph nodes, and at least one of the following criteria:
	  ○ grade 3 disease, or
	  ○ primary tumour size of at least 5 cm.

2	Lilly would like to make a general comment regarding the use of Abemaciclib in combination with endocrine therapy for the adjuvant treatment of hormone receptor positive HER2-negative early breast cancer at high risk of recurrence. The 5-year data from MonarchE was reported in the Rastogi et al paper in 2024.[1] According to Rastogi et al, "In the intent-to-treat population, with a median follow-up of 54 months, the benefit of abemaciclib was sustained with hazard ratios of 0.680 (95% CI, 0.599 to 0.772) for IDFS and 0.675 (95% CI, 0.588 to 0.774) for DRFS. This persistence of abemaciclib benefit translated to continuous separation of the curves with a deepening in 5-year absolute improvement in IDFS and DRFS rates of 7.6% and 6.7%, respectively, compared with rates of 6% and 5.3% at 4 years and 4.8% and 4.1% at 3 years." Consistent with the results in the ITT population are the IDFS (Invasive Disease Free Survival) and DRFS (Distant Relapse Free Survival) outcomes in Cohort 1(the population which is aligned with the marketing authorisation for Abemaciclib in the UK and with the current NICE TA). Detailed Findings (Cohort 1): **IDFS:** The hazard ratio (HR) for IDFS was 0.670 (95% CI, 0.588 to 0.764), indicating a 33% reduction in the risk of IDFS event. The absolute improvement in IDFS rates deepened at 5 years, reaching 7.9%. **DRFS:** The HR for DRFS was 0.665 (95% CI, 0.577 to 0.765), representing a 33.5% reduction in the risk of DRFS event. The absolute benefit in DRFS rates also deepened at 5 years, reaching 7.1%. In conclusion these outcomes reinforce confidence that Abemaciclib (in combination with endocrine therapy in the adjuvant setting for those patients with a high risk of recurrence) continues to reduce the risk of developing invasive and distant disease recurrence, well beyond the completion of the 2- year treatment duration. 1. Rastogi P 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 Mar 20;42(9):987-993
3	**3. 25 Managed Access** It was noted that further evidence collection in NATALEE could have the potential to address the uncertainties associated with immature data for people for which abemaciclib plus endocrine

NICE National Institute for Health and Care Excellence

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	treatment is not an option (population 5). However, the committee should consider the value of an additional 2 years of IDFS data that could resolve the considerable cost-effectiveness uncertainties for this population. Since a key driver is the estimates of patients moving into the DR health states, it could take considerably longer than the usual managed access period to inform these transitions given the natural course of disease progression from early to later stage breast cancer.
4	**3.5 Relevant NATALEE population for the cost effectiveness estimate for when abemaciclib is not an option** The cost-effectiveness estimates for population 5 is based on clinical effectiveness data from the full ITT population which includes both lymph-node positive and negative patients. It is not appropriate to use broader effectiveness data as a proxy for this population. Small changes in clinical effectiveness in early survival outcomes can cause considerable changes in downstream costs and outcomes in later stage advanced disease, therefore the committee should consider the generalisability of using proxy treatment effect data (ITT for population 5). The opportunity cost to consider is higher given the eligible population is potentially larger.
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Insert extra rows as needed

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- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[Insert organisation name]

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	nil
Name of commentator person completing form:	Michal Sladkowski

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	I agree that cost effectiveness results generated using population 5 would provide better data for patients where abemaciclib is not an option. However, based on NATALEE data, and as per the draft guidance: “ribociclib plus an aromatase inhibitor may provide an

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NICE National Institute for Health and Care Excellence

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	additional choice for people with hormone receptor-positive, HER2-negative, early-stage breast cancer at high risk of recurrence, particularly for people whose cancer does not meet the eligibility criteria for abemaciclib plus endocrine treatment.", Therefore, I would advise re-discussion with regards to eligibility criteria for adjuvant ribociclib, to better reflect NATALEE trial population; expanding it beyond patients who only meet abemaciclib eligibility criteria.
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Insert extra rows as needed

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Single Technology Appraisal

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

Comments on the draft guidance received through the NICE website

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	None
Notes	Not specified
Comments on the DG:	

Has all of the relevant evidence been taken into account?

1/ The 16 deaths triggered by Ribociclib toxicities reported in the FDA file and label, as well as in the EU label, have not been taken into account. Plus, we need to know how many more patients have died in the treated group from any cardiovascular toxicities since July 2023, because these are of course long-term events that continue to accrue post-treatment.

2/ [redacted], we need a sensitivity analysis adding 12-14 months of survival to all the mBC patients from the control group who were deprived of CDK4/6 inhibitors.
Novartis must also provide the table with the treatments given in first line therapy for each of the mBC patients in the control group, as well as in the exposed group where of course, adjuvant exposure to Ribociclib has then turned the patients resistant to this family of drugs and deprive them automatically from any benefit from this standard first line treatment when they become metastatic (mBC).

3/ Exact pourcentage of oestrogen and progesterone receptors in mBC patients in each group, given that Ribociclib aims to turn the patients to lose their receptors (as documented in Feline trial)

4/ Exact location of ALL the metastases in mBC patients in each group, given that Novartis [redacted] report only the least severe location when a patient develops several locations for their mBC. [redacted] in particular the brain and CNS locations triggered by the loss of the receptors triggered by Ribociclib adjuvant exposure.

5/ Informative censoring: Given the massive number of censored patients, especially in the control group, I ask Novartis to do the same as in MonarchE trial, where the investigators searched public databases to retreive the date of death of

the patients who died. And of course, if the public databases do not allow to find any record of death, the patient should be considered as still alive at the time of the search, at least in a sensitivity analysis, because otherwise, the overall survival is biaised between the two groups.

6/ Ask Novartis for the efficacy data in the group who dropped the treatment early, before may be one year of treatment (due to toxicity) versus the group who completed the three years of treatment. It is expected that the group who dropped treatment early could have developped less acquired resistance, although, since acquired resistance developp very quickly with ribociclib, as shown in the Ki67 of Feline and Coralleen trials, a difference may not be visible in Natalee victims.

7/ Among the patients exposed to ribociclib, what were the results for the group who had no progesterone receptors at diagnosis versus those who had some receptors at diagnosis. Same question for the non-exposed group?

8/
[redacted]. Moreover, you have noticed that the PI of Feline, Dr Qamar Khan, has cosigned an article with Ian Tannock and Antonio Fojo, two former presidents of ASCO, in the journal JCO, to explain that the patients should be preserved from adjuvant Ribociclib and asjuvant Abemaciclib, due to the acquired resistance phenomenon described in Feline trial, with an increased severity of the metastases explaining the discrepancy between OS and iDFS, plus all the biases (deprivation of the control group from access to CDK4/6 inhibitors, lost to follow-up, etc), and all the fatal adverse events and hospitalisations etc.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

It is of course completely fallacious to pretend that any efficacy will occur in OS, for the reasons explained above. Plus, it is completely unethical to pretend that the fatal adverse events in this population where most patients would never recurr, have the same "weight" as the deaths related to the disease. So many fatal adverse events in a healthy population are simply not acceptable at all.
[redacted]

The number of deaths triggered by Ribociclib in Natalee so far is already twice more than standard chemotherapy (0.6% versus 0.3%) and yet, Novartis is now launching many trials in Europe, NoLEETa trial,
[redacted]

Please read again the FDA file and label:
label: "Deaths due to AEs in the ribociclib+ET
arm was 0.6%, with deaths related to COVID-19 accounting for about 0.1%."

FDA file page 134: “It is important to note that patients with significant cardiac

history were excluded from NATALEE (as well as trials in the metastatic setting) but may be exposed to ribociclib in the post-market setting."

Page 159: "These benefits should not be extrapolated to the broader US population of patients with early-stage HR+, HER- breast cancer, most of whom are at considerably lower risk than patients enrolled to NATALEE. Clinical trials also represent idealized conditions and exclude many patients with comorbid conditions. Therefore, it will be important to continue to monitor this product in adjuvant use in the post-market setting where safety may differ."

Are the recommendations sound and a suitable basis for guidance to the NHS?

Not at all, the drug must not be reimbursed, and even if it was for free, it should not be given to any patient. It is not only perfectly inefficient on OS, but also, it caused many fatal adverse events in Natalee, and this will be even worse in real life setting due to the less healthy profile of the patients from the cardiovascular angle, and the fact that cardiovascular toxicities typically occur post-treatment, so nobody knows how many more deaths will occur in the coming years.

Also, an article from Tauber et al. (2025) has shown that [redacted], and that in reality, the patients eligible to Ribociclib will of course prefer Abemaciclib due to its much shorter treatment course, which means that in the end, Natalee trial is not at all representative of real life setting, as explained in the FDA file.

Plus, Novartis also denies the acquired resistance phenomenon, whereby the Ki67 increased from day 14 to day 180 in 73% of the patients in Coralleen (cf appendix of Pascual publication of 2024), and in 67% of the patients in Feline trial (cf publication by Griffiths et al from 2021). This clearly shows that this drug can not provide any control of the disease beyond a couple of weeks, and these acquired resistance mutations also mean that the endocrine treatment will become useless to control the recurrences. This is just scary. Plus, there is also a risk that the patients will lose their job due to this too long and exhausting treatment, or may simply decide to drop both Ribociclib and Letrozole, while you know that compliance to Letrozole is already very challenging on the long run. Adjuvant Ribociclib is just a pure non-sense from all angles that you could look at it. It only delays the occurence of mBC, but as seen with Niratinib, this does not mean any impact on OS, besides of a negative impact actually. Indeed, because of all the biases (deprivation of access to CDK4/6 inhibitors in the control group in case of mBC), we have actually a negative OS in the first few years of treatment: [redacted]. But now that Vinay Prasad entered the FDA, and given his previous publication against Natalee trial fallacies, I hope that the FDA will unreveal these fallacies. So, NICE should better wait and see, rather than to rush here... And you will see that you will not be the only ones to refuse [redacted]. Not only the Netherlands will follow you, but also the French, and I hope also Canada, Belgium, Switzerland, etc, because I have alerted everybody.

Are there any equality issues that need special consideration and are not covered in the medical technology consultation document?

some references:

Ian F. Tannock et al. Why We Do Not Recommend That Women With Breast Cancer Receive Adjuvant Treatment With a CDK4/6 Inhibitor. JCO 0, JCO-24-02683
DOI:10.1200/JCO-24-02683

Pascual, T., Fernandez-Martinez, A., Agrawal, Y. et al. Cell-cycle inhibition and immune microenvironment in breast cancer treated with ribociclib and letrozole or chemotherapy. npj Breast Cancer 10, 20 (2024). https://doi.org/10.1038/s41523-024-00625-7

Griffiths JI, Chen J, Cosgrove PA, O'Dea A, Sharma P, Ma C, Trivedi M, Kalinsky K, Wisinski KB, O'Regan R, Makhoul I, Spring LM, Bardia A, Adler FR, Cohen AL, Chang JT, Khan QJ, Bild AH. Serial single-cell genomics reveals convergent subclonal evolution of resistance as early-stage breast cancer patients progress on endocrine plus CDK4/6 therapy. Nat Cancer. 2021 Jun;2(6):658-671. doi: 10.1038/s43018-021-00215-7. Epub 2021 Jun 3. PMID: 34712959; PMCID: PMC8547038.

Tauber N, Hilmer L, Dannehl D, Fick F, Hemptenmacher F, Krawczyk N, Meyer-Lehnert T, Milewski K, Princk H, Hartkopf A, Rody A, Banys-Paluchowski M. Oral Maintenance Therapy in Early Breast Cancer-How Many Patients Are Potential Candidates? Cancers (Basel). 2025 Jan 5;17(1):145. doi: 10.3390/cancers17010145. PMID: 39796772; PMCID: PMC11720421.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	None
Notes	Not specified

Comments on the DG:

Has all of the relevant evidence been taken into account?

The evidence is dangerously distorded and biased for the following reasons:

A/ Article of Ian Tannock must be taken into account, all the more since his co-author Dr Khan is the lead investigator of Feline safety trial on Ribociclib in early breast cancer.

Tannock IF, Khan QJ, Fojo T. Why We Do Not Recommend That Women With Breast Cancer Receive Adjuvant Treatment With a CDK4/6 Inhibitor. J Clin Oncol. 2025 Apr 14:JCO2402683. doi: 10.1200/JCO-24-02683. PMID: 40228181.

B/ My comments on his article not taken into account, here-below:

Dear Professor Tannock, Doctor Khan and Doctor Fojo,

As a patient, I thank you for your insightful article(1) on the dangers of CDK4/6 inhibitors in early Breast Cancer (eBC). I will add some data to contextualize your article, and ask you one thing.

1/ Fatal adverse events attributed to these drugs, the data and the confusion

Fatal Adverse Events (AEs) were attributed to the investigational drug in 0.8% of the patients in MonarchE (2), and 0.6% in Natalee (as of July 2023): “Deaths due to AEs in the ribociclib+ET arm was 0.6%, with deaths related to COVID-19 accounting for about 0.1% (3)”. Among the 16 deaths, there is one road traffic accident (4), which is unusual. My reading is that Novartis should not ask us to stop driving for three years, as we not sick due to the disease, but exhausted by Ribociclib, which impairs our attention. The other deaths were driven by on-treatment and post-treatment cardiovascular events, and will be more frequent in real-life setting, as per regulatory warnings (5):

Page 134: “It is important to note that patients with significant cardiac history were excluded from NATALEE (as well as trials in the metastatic setting) but may be exposed to ribociclib in the post-market setting.”

Page 159: “These benefits should not be extrapolated to the broader US population of patients with early-stage HR+, HER- breast cancer, most of whom are at considerably lower risk than patients enrolled to NATALEE. Clinical trials also represent idealized conditions and exclude many patients with comorbid conditions. Therefore, it will be important to continue to monitor this product in adjuvant use in the post-market setting where safety may differ.”

While cardio-vascular events are typically long-term events (6-7), nobody knows how many more patients have died in Natalee trial since July 2023, and how many more will die in the future?

It is illegal to publish against the label. Yet, Novartis denied the regulatory causality assessment and [redacted] in their latest article in 2025 (8). [redacted] (9-10-11). These “no-death” claims also preclude any informed decision making, and any preventive safety measures.

In reality, this fatal toll of 0.6% is way beyond the “accepted” toll in eBC, where Taxanes and Anthracyclines trigger 0.3% of fatal adverse events all together, with immediate benefits on Overall Survival (OS), within two years (12-13). Yet, the investigators of Ribolaris, Calhys and Noleeta trials promote universal neoadjuvant and adjuvant Ribociclib, stating that “Both being too risky, Anthracyclines and Taxanes must be replaced by Ribociclib, a much safer, no-risk drug” (14-15).

2/ Subsequent treatments upon mBC, the data and the confusion in regulatory debates

Subsequent treatments are concealed in Natalee, but not in MonarchE (16). Their data show: i) in the treated arm, the acquired resistance to cdk4/6 inhibitors (and cross-resistance to other treatments (17));
[redacted] This bias attenuated the discrepancy between disease free survival and OS, appearing in the three trials (e.g. in Pallas, Hazard Ratio=1.32, 95% CI [0.98-1.78]) (18).

Due to this alarming discrepancy, with no efficacy on OS, and an aberrant fatal toll (0.8%), the Dutch authorities repeatedly refused Abemaciclib adjuvant treatment, defending a lawsuit (19-20). After three meetings, the French authorities approved it, besides of “no clinical added value” (21). The breast cancer expert reviewing the

treatments table downplayed the resistance issue (22), and the bias (control arm) (23). His manager promotes Noleeta and Ribolaris (24). Another expert replaced him recently (25); she reports to the French lead investigator of Ribolaris (26). Another breast cancer expert from his team will present the “cons” arguments (against Natalee/MonarchE) at the IFODS-ESMO congress (27). The Novartis-supported patient association will wrap-up the debate. Being a pharmacoepidemiologist patient of Prof André, I am denied access to the congress.

3/ Bias on lost to follow-up, the confusion

This bias is even leveraged in MonarchE: third parties are mandated to search public databases to recover OS on the patients lost to follow-up, but if no record of death appears anywhere, they remain coded as lost to follow-up (28). This aims to underestimate OS in the control arm, in case of more frequent lost to follow-up in the control arm. Sensitivity analyses should be provided.

4/ Acquired resistance triggering an inverse dose-effect relation in MonarchE, the data

In MonarchE, in Figure 1, the one-third of the treated arm with the lowest cumulative levels of drug exposure had the best outcomes (29). This group is driven by the patients who drop the drug very early, due to adverse effects, hence avoiding the dangerous period of acquired resistance. Prolonging the treatment from a relative dose intensity of “0-66%” towards “93% and above”, led to a striking drop in 3-year iDFS rates, from 91.2% [89.1%-92.9%] to 86.8% [84.4%-88.9%]. This shows how arbitrarily this long and aberrant duration of treatment is imposed to us.

5/ The acquired resistance in eBC reported in Feline trial is already confirmed since 2020

I respectfully disagree that Feline trial should get confirmed, since it is already confirmed by Coralleen trial. The authors did not see these data, given the way these data are concealed:

a/ Clinical progressions and Ki67 increases from Coralleen trial, confirming Feline trial

In Coralleen trial, Ribociclib triggered four progressions, two in lymph nodes, and two patients acquiring HER2+ status, versus no progression in the control arm (30). This statistically significant difference confirms the statistically significant differences reported in Feline trial (Figure 4d) (31).
Ribociclib triggered an increase in the Ki67 between day 14 and day 180 in 73% of Coralleen patients (32), via acquired resistance mechanisms. This is even higher than in Feline, as in Feline trial, half of the patients under Ribociclib had a continuous dosage at 400 mg, which appears slightly less detrimental than the cycles at 600 mg (difference appearing also in Leader trial (33)).

b/ Resistance mechanisms driving this 2-steps Ki67 dynamics

The Figure 6 in a poster of Nuria Chic shows a detrimental effect of Ribociclib on all the genes individually studied in Coralleen (34). This was dropped from the above article of Tomas Pascual.
Novartis supported both Feline and Coralleen phase 2 safety trials. They received

these data before any publication. My reading is that, after reading Feline trial data on acquired resistance,

[redacted], to confirm these acquired resistance mechanisms.

After confirming acquired resistance in Coralleen, Novartis launched a large neoadjuvant “me-too” program to replicate Feline at large scale, in elderly and premenopausal patients: Calhys (N=85), Ribolaris (N=1100) and Neoletrib (N=85). Internal control arms, Ki67 measures at day 14 and the “disappointing” Feline publications were dropped from the protocols and publications of the “me-too” trials (35-36-37). The last patient last visit in Feline was in April 2023, but, as of today, my investigators of the Novartis-supported “me-too” trials keep ignoring Feline 5-year OS data.

6/ One demand from myself, for Doctor Khan on your Feline Trial

New patients are enrolled every day in Ribolaris and Calhys, although I alerted all investigators and all authorities since August 2023, that universal neoadjuvant exposure to Ribociclib, [redacted] for the following reasons:

a/ Dr Khan did not include premenopausal women.

b/ By contrast to Ribolaris, Dr Khan also spared the women with a Ki67 above 10% at day 14.

c/ In Feline trial, half of the exposed arm received continuous Ribociclib (400 mg) instead of cycles (600 mg), which delayed slightly these acquired mutations of resistance (38).

d/ Dr Khan monitored tumor size via imaging exams each month, to offer surgery to women with an increasing size, including patients like me with an initial decrease followed by an increase, in my lymph node. This 2-step dynamics, and progressions in lymph nodes, are denied by Ribolaris investigators. They deny any obvious increase in size, refusing imaging. They delay surgery when asked by the patient: for two months for me. Another premenopausal patient with a superficial tumor of 1 cm was denied surgery at diagnosis. Upon her denied progression to 6 cm, she had to go to another site to get Platinium, and Pembrolizumab (as advised by Dr Chic (39)).
[redacted]. They acknowledge the most undeniable progressions in “only ~ 5%”, calling this rate a success, in patients initially eligible to surgery and chemotherapy (40).

e/ In Feline, chemotherapy was provided. In Ribolaris, half of us get denied chemotherapy, even premenopausal patients like me: I progressed, but I argued for standard chemotherapy.

f/ In Feline, the patients did not get Ribociclib beyond neoadjuvant exposure. In Ribolaris, the protocol states that neoadjuvant exposure aims
[redacted]

[redacted] We are not told about the early signs of the expected short-term and long-term cardiovascular toxicities, and our investigators refuse to advocate for vaccination, [redacted] that Ribociclib has “no clinically meaningful impact on immunity”.

g/ Next Generation Sequencing (NGS) tests are recommended in clinical trials upon progression triggered by acquired resistance to CDK4/6, for prognosis, and to identify therapeutic targets (42). Yet, after acquired resistance triggered by neoadjuvant Ribociclib in most of us, BCRF is funding “genomic signatures” for Ribolaris [redacted] (43), against the standard-of-care NGS for clinical trials.

By contrast with Neoletrib protocol (44), I was not either granted neoadjuvant rescue treatments. Prof André agreed to grant me access to several off-label drugs, such as Fulvestrant, based on my NGS, that Novartis refused to pay. Yet, he keeps refusing any of these rescue drugs to all the other patients, whom he keeps under Ribociclib, as of today. In this context, I beg you, Dr Khan, to disclose publicly, now, your study report on clinicaltrials.gov, with your 5-year OS data.

Thank you in advance for your sustained commitment towards ethics and transparency,

Respectfully,

[redacted]

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https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/208716s019lbl.pdf

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https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/209092s018lbl.pdf

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See Table 64 page 108, and Unfavorable Effects page 123, for the 16 deaths due to Ribociclib toxicities:
https://www.ema.europa.eu/en/documents/variation-report/kisqali-h-c-004213-ii-0045-epar-assessment-report-variation_en.pdf

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Page 13. CONTROVERSES ET RECOMMANDATIONS PRATIQUES EN SÉNOLOGIE EN 2025 : LES DONNÉES QUI DOIVENT GUIDER LA DÉCISION EN RCP !
Inhibiteurs de CDK 4/6 en situation adjuvante pour toutes les patientes à risque pNO ou pN+

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Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The effectiveness is fully biaised: the product only delays the onset of the metastases, as was seen already in eBC with Neratinib for instance, but it does not cure anybody, due to the increase in the severity of the metastases triggered by Ribociclib exposure via acquired resistances and mutations (cf Feline trial).
The false signal reported on overall survival [redacted].

Moreover, there is a massive and unacceptable toxicity leading to 16 deaths as of July 2023, as explained in my above comments.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Not at all, in their current presentation, the recommendations will preclude any informed decision making and lead the patients to falsely believe in the fallacious claims of Novartis about a "no risk drug, with no death", and about a drug capable to save any lives, which the data do not show at all. It could well be that the above bias on access to treatments in case of mBC, in fact hides that Ribociclib triggers more deaths in the treated arm, as seen in Pallas trial for instance.

Are there any equality issues that need special consideration and are not covered in the medical technology consultation document?

Of course, see above issues. Nobody should get exposed to Ribociclib in early Breast Cancer in such an uninformed and unethical way. You should also inform the patients of the ongoing, upcoming and past trials. Thank you in advance for your sense of ethics, please.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	None
Notes	Not specified

Comments on the DG:

Section - 1 Recommendations, 1.1

Please could you consider widening the criteria of eligibility. For example, to those with node positive disease but other high risk features such as lymphovascular invasion, extra capsular LN disease or multi-focal cancer (e.g. largest tumour size less than 5 cm but combination size of all tumours at least 5 cm). Thank you.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	None
Notes	Not specified

Comments on the DG:

Has all of the relevant evidence been taken into account?

NO. The report of the NATALEE trial makes the results uninterpretable. The amount of censoring from the arms of the trial dwarfs the reported difference in its primary endpoint (iDFS). Please see our paper:
Tannock IF, Khan QJ, Fojo T. Why We Do Not Recommend That Women With Breast Cancer Receive Adjuvant Treatment With a CDK4/6 Inhibitor. J Clin Oncol. 2025:JCO2402683. doi: 10.1200/JCO-24-02683.
I did a word search on your report and "censoring" is not even mentioned.
Also there are 2 smaller studies indicating that early exposure to ribociclib may accelerate resistance to endocrine therapy, neither of which are referenced.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

NO - the benefits of adjuvant ribociclib are unknown. It is toxic and there was no reason for prescribing 3 years of therapy - resistance occurs earlier on the metastatic setting. It is as likely to cause harm to British women with breast cancer as to lead to benefit.
There is no difference in survival (admittedly follow-up is early) in the NATALEE trialbut with the unknown vital status of ~20% of patients that will never be known.
Failure to fund a cdk4/6 inhibitor for relapsing controls in this global trial also

creates an obvious bias in favour of the experimental arm even if an apparent difference in survival eventually emerges.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No - The recommendations are not appropriate. The committee should reevaluate the trial results in light of the excessive duration of treatment, the huge amounts of censoring leading to unknown outcomes, the failure for relapsing controls to be treated with SOC treatment, and the emerging evidence that exposure to ribociclib may promote resistance to endocrine therapy.

Are there any equality issues that need special consideration and are not covered in the medical technology consultation document?

No

EAG PRE-ACM2 APPENDIX

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

Pre-ACM2 Appendix: EAG critique of Population 5 evidence submitted by the company following publication of NICE Draft Guidance

This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR136255

Completed 30 May 2025

CONTAINS CONFIDENTIAL DATA

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 INTRODUCTION

Cost effectiveness estimates for ribociclib with an aromatase inhibitor (ribociclib+AI) for adjuvant treatment of hormone receptor-positive (HR-positive), human epidermal growth factor receptor 2-negative (HER2-negative) early breast cancer at high risk of recurrence were presented in the company submission (CS) for four populations:

- Population 1 (NATALEE trial intention-to-treat [ITT] population)
- Population 2 (node-positive disease)
- Population 3 (node-negative disease)
- Population 4 (patients with node-positive breast cancer at high risk of recurrence who are eligible for treatment with abemaciclib+ET).

The External Assessment Group (EAG) considered that Population 4 (patients eligible for abemaciclib+ET) and an additional population, patients ineligible for abemaciclib+ET (Population 5) were the most relevant populations for this appraisal and asked the company to provide cost effectiveness estimates for these two populations (clarification question B1). The company did not provide Population 5 cost effectiveness results as they considered 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". The EAG therefore used Population 1 cost effectiveness results as a proxy for Population 5 cost effectiveness results.

Following National Institute for Health and Care Excellence (NICE) Appraisal Committee Meeting 1 (ACM1), the NICE Appraisal Committee (AC) recommended ribociclib+AI as an adjuvant treatment option for Population 4 only.[1] The NICE AC did not recommend ribociclib+AI as an adjuvant treatment option for Population 5 because "…there was not enough evidence to show cost effectiveness of [ribociclib+AI]" for Population 5 and because there were "…uncertainties about some assumptions used in the economic model".[1] In response to the NICE Draft Guidance, the company provided cost effectiveness estimates for Population 5.[2] NICE asked the EAG to review the company Population 5 cost effectiveness estimates and modelling assumptions.

This appendix includes the EAG's critique of the company's Population 5 cost effectiveness evidence. This evidence was provided by the company in response to the NICE Draft Guidance[2] and was generated using the model that was submitted to NICE on 29 May 2025.

1.1 Company Population 5 base case assumptions

The company Population 5 base case analysis incorporated a mixture of the NICE ACM1 preferred assumptions, the company's original modelling assumptions and new data that related specifically to Population 5, namely invasive disease-free survival (iDFS), time to treatment discontinuations (TTD), and AE incidence data; these data were sourced from the NATALEE trial. Population 5 NICE AC preferred assumptions, company base case assumptions and company scenarios are presented in Table 1.

Table 1 Company Population 5 base case assumptions and NICE AC preferred assumptions

Parameter		NICE AC preferred assumption	Company base case	Company scenarios
iDFS extrapolations (Population 5)	Ribociclib	-	Gamma (R)	Log-Logistic (R) Weibull (R) Lognormal (R) Gompertz (R) RCS Weibull (R) RCS Log-Logistic (R) Gen. Gamma (R) Gen. F (R)
	AI (in combination with ribociclib)	-	Gamma (R)	
	ET	-	Gamma (R)	
TTD extrapolations (Population 5)	Ribociclib	-	NATALEE trial K-M data	-
	AI (in combination with ribociclib)	-	Weibull (R)	
	ET	-	Weibull (R)	
Adverse events	Ribociclib	-	Alanine aminotransferase increased: [redacted] Neutropenia: [redacted]	-
	ET	-	Alanine aminotransferase increased: [redacted] Neutropenia: [redacted]	-
iDFS treatment effect waning		Accept company approach (constant treatment effect for 8 years followed by waning until ribociclib iDFS hazard rate reaches general mortality hazard rate) but would like to see a wider range of treatment-waning scenarios	As per committee preferred assumption	Constant treatment effect for 8 years, followed by treatment waning for: • 17.5 years • 15 years • 12.5 years • 10 years • 7.5 years • 5 years
iDFS event distribution	-	iDFS event proportions for all treatments are equal	NATALEE trial ITT population pooled events (updated 29 May 2025)	-

Parameter		NICE AC preferred assumption	Company base case	Company scenarios
PFS and OS in the ET-resistant and ET-sensitive DR sub-states	ET-sensitive PFS	Exponential	Lognormal	• GenGamma Exponential
	ET-sensitive OS	Gamma	Log-logistic	• Average of log-logistic and Gamma • Gamma
	ET-resistant PFS	Exponential	Lognormal (R)	• Average of lognormal (R) and exponential • Exponential
	ET-resistant OS	Weibull (R)	Loglogistic (R)	• RCS lognormal (U) • Weibull (R)
Treatment mix: DR substate	ET-resistant and CDK 4/6 inhibitor-sensitive	90% of people would have retreatment with CDK 4/6 inhibitors	60% of people would have retreatment with CDK 4/6 inhibitors	75% and 90%
	ET-sensitive and CDK 4/ sensitive 6 inhibitor-sensitive	90% of people would have retreatment with CDK 4/6 inhibitors	As per NICE AC preferred assumption	-
PFS utility value in ET-sensitive DR sub-state	-	NMR health-state utility value	As per NICE AC preferred assumption	-

AC=appraisal committee; AI=aromatase inhibitor; CDK=cyclin-dependent kinases; DR=distant recurrence; ET=endocrine therapy; iDFS=invasive disease-free survival; ITT=intention to treat; NICE=National Institute for Health and Care Excellence; NMR=non-metastatic recurrence; OS=overall survival; PFS=progression-free survival; R=restricted; RCS=radar cross section; TTD=time to treatment discontinuation; U=unrestricted

1.2 EAG critique of company modelling assumptions

1.2.1 General mortality rate not incorporated into iDFS transition probabilities

The EAG considers that the company inappropriately accounted for the general mortality rate when calculating transition probabilities from the fitted iDFS curve. In the base case, the general mortality rate was included in addition to the iDFS event rate, rather than incorporated into it. This means that the hazard rate used to calculate model results is always higher than the hazard rate associated with the chosen curve and that the hazard increases over time. The EAG has revised the transition probability calculations to incorporate the general mortality rate within the fitted iDFS curve cycle probability (Table 2).

Table 2 Company and EAG approaches to calculating iDFS transition probabilities incorporating general mortality rates

Destination state from iDFS	Company cycle hazard calculation	EAG cycle hazard calculation[a]
Death	Change in iDFS multiplied by proportion of events that are deaths ([redacted]% per cycle)	***iDFS hazard > general mortality hazard:*** Change in iDFS multiplied by proportion of events that are deaths ([redacted]% per cycle), plus general mortality ***iDFS hazard ≤ general mortality hazard:*** general mortality
NMR	Change in iDFS multiplied by proportion of events that are NMR ([redacted]% per cycle)	***iDFS hazard > general mortality hazard:*** Change in iDFS multiplied by proportion of events that are NMR out of the events that are not death events ([redacted]% per cycle) ***iDFS hazard ≤ general mortality hazard:*** 0
DR	Change in iDFS multiplied by proportion of events that are DR ([redacted]% per cycle)	***iDFS hazard > general mortality hazard:*** Change in iDFS multiplied by proportion of events that are DR out of the events that are not death events ([redacted]% per cycle) ***iDFS hazard ≤ general mortality hazard:*** 0
SPM	Change in iDFS multiplied by proportion of events that are SPM ([redacted]% per cycle)	***iDFS hazard > general mortality hazard:*** Change in iDFS multiplied by proportion of events that are SPM out of the events that are not death events ([redacted]% per cycle) ***iDFS hazard ≤ general mortality hazard:*** 0

[a] The proportion of events that are NMR, DR or SPM are calculated from the company event rates weighted by the proportion of events that are not death events ([redacted]%)

DR=distant recurrence; EAG=External Assessment Group; iDFS=invasive disease-free survival; NMR=non-metastatic recurrence; SPM=second primary malignancy

1.2.2 iDFS extrapolations

The company's fitted parametric curves yield a wide variety of long-term iDFS estimates for both patients treated with ribociclib+AI and those treated with endocrine therapy (ET). In the base case, the company chose Gamma distributions to generate long-term iDFS estimates. The company base case iDFS curves (which include base case general mortality adjustments for both treatments and treatment effect waning for ribociclib+AI) are shown in Figure 1. The full suite of curves presented by the company are provided in Appendix 1, Section 2.1.

Figure 1 Company base case Population 5 iDFS distributions (including general mortality adjustments and base case treatment effect waning)

AI=aromatase inhibitor; ET=endocrine therapy; iDFS=invasive disease-free survival; K-M=Kaplan-Meier; R=restricted
Source: Company response to NICE Draft Guidance,[2] Appendix B.3)

Based on inspection of the NATALEE trial Population 5 iDFS Kaplan-Meier (K-M) data, the company assumed that the [redacted]. These data are very immature (number of events at data cut off: ribociclib+AI=[redacted], ET=[redacted]; company response to NICE Draft Guidance,[2] Figure 2) and therefore patterns in long-term relative hazards (ribociclib+AI and ET) may not yet be apparent and current proportionality test results may not hold in the long-term. Further, although the company states that it considers the[redacted](company response to NICE Draft Guidance,[2] Appendix B.3), the company has fitted parametric distributions to each arm independently. The company has presented 'pairs' of curves of the same distribution; however, these curves were not fitted using treatment as a covariate and therefore hazard ratios (HRs) are not reported in the

company response to NICE Draft Guidance,[2] nor are any HRs explicitly presented as company model inputs.

Given the substantial differences in long-term iDFS estimates for patients treated with ribociclib+AI and those treated with ET that are generated by the distributions considered by the company and the lack of long-term data to support base case curve choices, the EAG has presented four alternative scenarios; scenario results have been generated using lower and upper plausible bound for incremental iDFS when assuming:

1. the same parametric distribution is appropriate for both intervention and comparator and
2. different parametric distributions are chosen for each comparator.

The EAG scenarios represent the largest difference and the smallest difference in mean survival time. The mean difference in survival time for each pair of curves – including EAG adjustments for general mortality but without additional treatment effect waning assumptions – are shown in

Table 3. Cells shaded in light grey represent results when the same parametric distributions were chosen for both treatments. Cells shaded in dark grey represent the curve pairs used in the EAG scenarios.

Table 3 Difference in mean survival times for 'pairs' of iDFS curves in company model (including general mortality adjustment, excluding treatment effect waning)

Years		Ribociclib+AI[a]									
		Exponential	**Gamma**	**Gen. F**	**Gen. gamma**	**Gomp**	**Log-log**	**Lognorm**	**RCS Log-log**	**RCS Weibull**	**Weibull**
ET[a]	**Exponential**	2.9	1.0	2.4	2.4	-	1.7	-	2.4	1.8	**0.7**
	Gamma	5.3	3.4	4.8	4.8	-	4.1	-	4.8	4.2	3.1
	Gen. F	3.0	1.1	2.4	2.4	-	1.8	-	2.5	1.9	0.7
	Gen. gamma	3.0	1.1	2.4	**2.4**	-	1.8	-	2.5	1.9	0.7
	Gomp	-	-	-	-	-	-	-	-	-	-
	Log-log	3.9	2.0	3.4	3.4	-	2.7	-	3.4	2.8	1.7
	Lognorm	1.2	-	0.7	0.7	-	-	-	0.7	-	-
	RCS Log-log	3.1	1.2	2.5	2.5	-	1.9	-	2.6	2.0	0.8
	RCS Weibull	4.4	2.5	3.9	3.9	-	3.2	-	3.9	3.3	2.2
	Weibull	**5.9**	4.0	5.4	5.4	-	4.7	-	5.4	4.8	**3.7**

[a] All curves are restricted
AI=aromatase inhibitor; ET=endocrine therapy; iDFS=invasive disease-free survival

For pragmatic purposes, the EAG accepts the company assertion that the 20 year iDFS for the Gompertz (R) distribution is unlikely to be clinically plausible, so these curves have been excluded from the EAG scenarios. The lognormal curve for ribociclib+AI is also not included in the EAG scenarios as, when combined with the EAG approach to incorporating general mortality, all iDFS events are death events for the whole model time horizon. Finally, mean survival time results from ribociclib+AI and ET distributions that crossed were also excluded from the EAG scenarios. The distributions used in the EAG scenarios are presented in Table 4. The resulting curves for each scenario are included in Appendix 1, Section 2.1 to Appendix 6, Section 2.6.

Table 4 Parametric distributions used to generate EAG scenario results

Parametric distribution	Upper bound	Lower bound
Same for intervention and comparator	Weibull (R)	Generalised gamma (R)
Different for intervention and comparator	Ribociclib+AI: exponential ET: Weibull (R)	Ribociclib+AI: Weibull ET: exponential (R)

AI=aromatase inhibitor; EAG=External Assessment Group; ET=endocrine therapy; R=restricted

1.2.3 Treatment effect waning scenarios

The EAG has presented cost effectiveness results for the longest (8 years constant treatment effect plus 17.5 years waning) and shortest (8 years constant treatment effect plus 5 years waning) treatment effect waning scenarios included in the company DG response (Table 8).

1.2.4 PFS and OS extrapolations in DR health state

The EAG considers the NICE ACM1 preferred distributions remain the most appropriate options to use to estimate PFS and OS in the DR health state for Population 5.

1.2.5 Treatment mix in the ET-resistant CDK4/6-sensitive treatment substate following treatment with ribociclib+AI

The company has presented further clinical opinion regarding the likelihood… of re-treatment with a CDK4/6 inhibitor. There is no indication of consensus amongst the clinical experts consulted by the company and nor does the opinion clearly suggest that the NICE ACM1's preferred assumption should be updated. The EAG has therefore retained the NICE ACM1 preferred assumption, i.e., that 90% of patients would be retreated with a CDK4/6 inhibitor; this matches the proportion of patients who receive a CDK4/6 inhibitor following treatment with ET.

1.3 Impact of EAG amendments on the company base case results

The EAG has generated cost effectiveness results (using the company Population 5 model) by making the revisions presented in Table 5 and running the scenarios presented in

Table 6.

Table 5 EAG model revisions

EAG revisions
R1) NICE ACM1 preferred: PFS and OS in DR health state
R2) NICE ACM1 preferred: treatment mix ET-resistant substate
B1. Company base case adjusted to include NICE ACM1 preferred assumptions
B2. B1 adjusted for iDFS general mortality calculation

ACM1=Appraisal Committee Meeting 1; DR=disease recurrence; EAG=External Assessment Group; ET=endocrine therapy; iDFS=invasive disease-free survival; NICE=National Institute for Health and Care Excellence; OS=overall survival; PFS=progression-free survival

Table 6 EAG scenarios

EAG scenarios
S1) B2+iDFS lower mean difference: Gen. gamma (R)
S2) B2+iDFS upper mean difference: Weibull (R)
S3) B2+iDFS lower mean difference: Weibull (ribociclib+AI), exponential (R) (ET)
S4) B2+iDFS upper mean difference: exponential (ribociclib+AI), Weibull (R) (ET)
S5) B2+treatment effect waning: 8 years constant, 5 years waning
S6) B2+treatment effect waning: 8 years constant, 17.5 years waning
Combined EAG scenarios
S7) S1+S5
S8) S1+S6
S9) S2+S5
S10) S2+S6
S11) S3+S5
S12) S3+S6
S13) S4+S5
S14) S4+S6

AI=aromatase inhibitor; EAG=External Assessment Group; ET=endocrine therapy; iDFS=invasive disease-free survival; (R)=restricted

Deterministic cost effectiveness results for pairwise comparisons (ribociclib+AI versus ET) are provided in Table 8. All results have been generated using 2023 list prices for all drugs except for ribociclib and alpelisib (Patient Access Scheme prices). These analyses have been replicated using confidential prices (see Table 7); results from these analyses are provided in Confidential Pre-ACM2 Appendix.

Table 7 Sources of prices used in the EAG confidential appendix

Treatment	Price source/type of commercial arrangement
Ribociclib	PAS
Abemaciclib	PAS
Alpelisib	PAS
Palbociclib	PAS
Letrazole	eMIT
Anastrazole	eMIT
Exemestane	eMIT
Zoledronic acid	eMIT
Tamoxifen	eMIT
Everolimus	eMIT
Fulvestrant	eMIT
Paclitaxel	eMIT
Capecitabine	eMIT
Gosrelin	BNF

BNF=British National Formulary; EAG=External Assessment Group; eMIT=electronic Market Information Tool; PAS=Patient Access Scheme
Source: price tracker form (November 2024)

Table 8 Deterministic pairwise results (ribociclib+AI versus ET, Population 5), PAS prices for ribociclib and alpelisib

EAG revisions	Ribociclib+AI		ET		Incremental		ICER £/QALY	NMB[a]
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A1. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R1) NICE ACM1 preferred: PFS and OS in DR health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R2) NICE ACM1 preferred: treatment mix ET-resistant substate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B1. Company base case adjusted to include NICE ACM1 preferred assumptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B2. B1 adjusted for iDFS general mortality calculation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S1) B2+iDFS lower mean difference: Gen. gamma (R)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S2) B2+iDFS upper mean difference: Weibull (R)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S3) B2+iDFS lower mean difference: Weibull (ribociclib+AI), exponential (R) (ET)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S4) B2+iDFS upper mean difference: exponential (ribociclib+AI), Weibull (R) (ET)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S5) B2+treatment effect waning: 8 years constant, 5 years waning	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S6) B2+treatment effect waning: 8 years constant, 17.5 years waning	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Combined EAG scenarios	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S7) S1+S5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S8) S1+S6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S9) S2+S5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S10) S2+S6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S11) S3+S5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S12) S3+S6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S13) S4+S5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S14) S4+S6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] WTP threshold of £30,000

ACM1=Appraisal Committee Meeting 1; 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

2 APPENDICES

2.1 Appendix 1: Company fitted Population 5 iDFS curves including base case general mortality adjustments

Figure 2 Company fitted Population 5 iDFS curves: ribociclib+AI, including general mortality, no treatment effect waning

iDFS=invasive disease-free survival; R=restricted; ribo+AI=ribociclib with an aromatase inhibitor
Source: company model (29 May 2025)

Figure 3 Company fitted Population 5 iDFS curves: ribociclib+AI, including general mortality, base case treatment effect waning

iDFS=invasive disease-free survival; R=restricted; ribo+AI=ribociclib with an aromatase inhibitor
Source: company model (29 May 2025)

Figure 4 Company fitted Population 5 iDFS curves: ET, including general mortality

ET=endocrine therapy; iDFS=invasive disease-free survival; R=restricted; RCS=radar cross section
Source: company model (29 May 2025)

2.2 Appendix 2: EAG iDFS scenarios

2.2.1 Company base case iDFS distributions

Figure 5 Company base case iDFS distributions, base case treatment effect waning (EAG general mortality adjustment)

EAG=External Assessment Group; ET=endocrine therapy; iDFS=invasive disease-free survival; K-M=Kaplan-Meier; R=restricted; ribo+AI=ribociclib with an aromatase inhibitor
Source: EAG amended company model (29 May 2025 version)

Figure 6 Company base case iDFS distributions, lower treatment effect waning scenario (EAG general mortality adjustment) [EAG S5]

EAG=External Assessment Group; ET=endocrine therapy; iDFS=invasive disease-free survival; K-M=Kaplan-Meier; R=restricted; ribo+AI=ribociclib with an aromatase inhibitor
Source: EAG amended company model (29 May 2025 version)

Figure 7 Company base case iDFS distributions, upper treatment effect waning scenario (EAG general mortality adjustment) [EAG S6]

EAG=External Assessment Group; ET=endocrine therapy; iDFS=invasive disease-free survival; K-M=Kaplan-Meier; R=restricted; ribo+AI=ribociclib with an aromatase inhibitor
Source: EAG amended company model (29 May 2025 version)

2.3 Appendix 3: EAG lower mean survival time difference, matching iDFS distributions

Figure 8 EAG lower mean survival time difference, matching iDFS distributions, base case treatment effect waning (EAG general mortality adjustment) [EAG S1]

EAG=External Assessment Group; ET=endocrine therapy; iDFS=invasive disease-free survival; K-M=Kaplan-Meier; R=restricted; ribo+AI=ribociclib with an aromatase inhibitor
Source: EAG amended company model (29 May 2025 version)

Figure 9 EAG lower mean survival time difference, matching iDFS distributions, lower treatment effect waning scenario (EAG general mortality adjustment) [EAG S7]

EAG=External Assessment Group; ET=endocrine therapy; iDFS=invasive disease-free survival; K-M=Kaplan-Meier; R=restricted; ribo+AI=ribociclib with an aromatase inhibitor
Source: EAG amended company model (29 May 2025 version)

Figure 10 EAG lower mean survival time difference, matching iDFS distributions, higher treatment effect waning scenario (EAG general mortality adjustment) [EAG S8]

EAG=External Assessment Group; ET=endocrine therapy; iDFS=invasive disease-free survival; K-M=Kaplan-Meier; R=restricted; ribo+AI=ribociclib with an aromatase inhibitor
Source: EAG amended company model (29 May 2025 version)

2.4 Appendix 4: EAG upper mean survival time difference, matching iDFS distributions

Figure 11 EAG upper mean survival time difference, matching iDFS distributions, base case treatment effect waning (EAG general mortality adjustment) [EAG S2]

EAG=External Assessment Group; ET=endocrine therapy; iDFS=invasive disease-free survival; K-M=Kaplan-Meier; R=restricted; ribo+AI=ribociclib with an aromatase inhibitor
Source: EAG amended company model (29 May 2025 version)

Figure 12 EAG upper mean survival time difference, matching iDFS distributions, lower treatment effect waning scenario (EAG general mortality adjustment) [EAG S9]

EAG=External Assessment Group; ET=endocrine therapy; iDFS=invasive disease-free survival; K-M=Kaplan-Meier; R=restricted; ribo+AI=ribociclib with an aromatase inhibitor
Source: EAG amended company model (29 May 2025 version)

Figure 13 EAG upper mean survival time difference, matching iDFS distributions, higher treatment effect waning scenario (EAG general mortality adjustment) [EAG S10]

EAG=External Assessment Group; ET=endocrine therapy; iDFS=invasive disease-free survival; K-M=Kaplan-Meier; R=restricted; ribo+AI=ribociclib with an aromatase inhibitor
Source: EAG amended company model (29 May 2025 version)

2.5 Appendix 5: EAG lower mean survival time difference, independent iDFS distributions

Figure 14 EAG lower mean survival time difference, independent iDFS distributions, base case treatment effect waning (EAG general mortality adjustment) [EAG S3]

EAG=External Assessment Group; ET=endocrine therapy; iDFS=invasive disease-free survival; K-M=Kaplan-Meier; R=restricted; ribo+AI=ribociclib with an aromatase inhibitor
Source: EAG amended company model (29 May 2025 version)

Figure 15 EAG lower mean survival time difference, independent iDFS distributions, lower treatment effect waning scenario (EAG general mortality adjustment) [EAG S11]

EAG=External Assessment Group; ET=endocrine therapy; iDFS=invasive disease-free survival; K-M=Kaplan-Meier; R=restricted; ribo+AI=ribociclib with an aromatase inhibitor
Source: EAG amended company model (29 May 2025 version)

Figure 16 EAG lower mean survival time difference, independent iDFS distributions, higher treatment effect waning scenario (EAG general mortality adjustment) [EAG S12]

EAG=External Assessment Group; ET=endocrine therapy; iDFS=invasive disease-free survival; K-M=Kaplan-Meier; R=restricted; ribo+AI=ribociclib with an aromatase inhibitor
Source: EAG amended company model (29 May 2025 version)

2.6 Appendix 6: EAG upper mean survival time difference, independent iDFS distributions

Figure 17 EAG upper mean survival time difference, independent iDFS distributions, base case treatment effect waning (EAG general mortality adjustment) [EAG S4]

EAG=External Assessment Group; ET=endocrine therapy; iDFS=invasive disease-free survival; K-M=Kaplan-Meier; R=restricted; ribo+AI=ribociclib with an aromatase inhibitor
Source: EAG amended company model (29 May 2025 version)

Figure 18 EAG upper mean survival time difference, independent iDFS distributions, lower treatment effect waning scenario (EAG general mortality adjustment) [EAG S13]

EAG=External Assessment Group; ET=endocrine therapy; iDFS=invasive disease-free survival; K-M=Kaplan-Meier; R=restricted; ribo+AI=ribociclib with an aromatase inhibitor
Source: EAG amended company model (29 May 2025 version)

Figure 19 EAG upper mean survival time difference, independent iDFS distributions, higher treatment effect waning scenario (EAG general mortality adjustment) [EAG S14]

EAG=External Assessment Group; ET=endocrine therapy; iDFS=invasive disease-free survival; K-M=Kaplan-Meier; R=restricted; ribo+AI=ribociclib with an aromatase inhibitor
Source: EAG amended company model (29 May 2025 version)

3 REFERENCES

1. 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]. Draft guidance consultation. 24 April 2025; Available from: https://www.nice.org.uk/guidance/gid-ta11090/documents/draft-guidance. Accessed 22 May 2025.
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