Medicinrådet

Bilag til Medicinrådets vurdering af ribociclib (Kisqali®) som adjuverende behandling af ER+/HER2-negativ brystkræft

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. adjuverende ribociclib
2. Amgros' forhandlingsnotat vedr. adjuverende ribociclib
3. Ansøgning vedr. adjuverende ribociclib

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Medicinrådet
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7. August 2025

Notat til Medicinrådets udkast til anbefaling vedr. ribociclib i kombination med en aromatasehæmmer til adjuverende behandling af tidlig ER+/HER2-negativ brystkræft

Vi ønsker at kommentere Medicinrådets udkast til anbefaling, som foreslår at begrænse adgangen af ribociclib til udelukkende de patienter, der opfylder kriterierne for monarchE-populationen. En sådan anbefaling er mere restriktiv end alle vores nabolande, herunder Sverige, Storbritannien og Finland, hvor der allerede er givet adgang til hele NATALEE-populationen. Her skal det særligt fremhæves, at NICE har vurderet non-monarchE subgruppen seperat både på kliniske data samt fuld sundhedsøkonomisk vurdering og på denne baggrund fundet ribociclib omkosningseffektivt og givet fuld adgang. I vurderingen fandt NICE ligeledes, at der er usikkerheder i datagrundlaget, men fandt disse rimelige set i lyset af patienternes dårlige prognose med behov for yderligere behandling. [redacted]. Følges udkast til anbefalingen, vil Danmark aktuelt være det eneste land i Europa, der begrænser ribociclib's anvendelse indenfor tidlig brystkræft indikationen.

Indsigelser mod begrænsning af adgang til ribociclib for non-monarchE-patienter (PICO 2):
Medicinrådets vurdering er primært baseret på bekymringer om datamodenhed og en begrænset absolut effekt i non-monarchE-populationen. Vi mener dog, at følgende punkter bør overvejes yderligere:

1. **Relativ risikoreduktion:**
   Vurderingsrapporten anerkender ribociclibs statistisk signifikante relative risikoreduktion for sygdomstilbagefald (IDFS og DRFS), men vægter effekten lavt på grund af den moderate absolutte risikoreduktion. Relativ risikoreduktion er dog en afgørende parameter, særligt for patientgrupper med forskellige baseline-risici. At minimere dens betydning kan føre til oversete kliniske fordele, som ofte tydeliggøres ved længere opfølgningstider – en proces, der allerede er set og dokumenteret i NATALEE og monarchE studierne, hvor data-cuts med længere opfølgningstid konsistent har vist samme relative risiko, men med øget absolut risiko reduktion over tid.

2. **Klinisk relevans:**
   Non-monarchE-patienterne har stadig en betydelig risiko for tilbagefald, hvilket underbygges af DBCG-data (7-årig DRFS på [redacted] for højrisiko N0-patienter og [redacted] for non-monarchE samlet). Ribociclibs dokumenterede evne til at reducere DRFS ([redacted]) kan derfor forhindre et betydeligt antal tilbagefald ([redacted]). Denne effekt bør betragtes som klinisk meningsfuld.

3. **Forskelsbehandling af patienter med høj riskiko for tilbagefald:**
   Den binære opdeling i monarchE- og non-monarchE-patienter oversimplificerer risikoprofilen inden for begge grupper. For eksempel vil en patient med højrisiko T4N0-sygdom ekskluderes fra adgang til ribociclib, mens en T0N1-patient med relativt lavere risko kvalificerer sig til behandling, udelukkende fordi den ene tilhører monarchE og den anden non-monarchE. Denne forskelsbehandling er problematisk og kontraintuitiv, især i betragtning af at ribociclibs relative risikoreduktion er konsistent på tværs af alle subgrupper, med fordele afledt proportionalt af den enkelte patients baseline-risikoniveau.

4. **Udfordringer ved identificering af monarchE-patienter i dansk klinisk praksis**
   Det er problematisk, at anbefalingen for ribociclib baseres på monarchE-gruppen, da ændringer i dansk klinisk praksis (SENOMAC-praksis) gør det vanskeligt at identificere patienter med N2-3 sygdom (≥ 4 positive lymfeknuder), som ellers udgør en central del af monarchE-populationen. Med den nuværende

praksis udføres der hos udvalgte patienter kun sentinel node (SN)-operation og ikke længere aksilrømning, hvilket betyder, at det samlede antal positive lymfeknuder ofte ikke registreres. Konsekvensen er, at læger ikke kan stadieinddele patienterne med sikkerhed, og mange patienter med N2-3 sygdom risikerer at gå uidentificerede i dansk klinisk praksis. På den anden side tilbyder ribociclib indikationen en bredere population end abemaciclib, da behandlingen omfatter højrisiko N0-patienter og patienter med N1-sygdom, som kan identificeres uden krav om præcis lymfeknudestatus. Denne tilgang gør ribociclib og NATALEE inklusionskritierne mere anvendelig i Danmark under de nuværende kirurgiske procedurer. Derfor er det stærkt uhensigtsmæssigt at underlægge ribociclibs adgang monarchE-kriteriene, da de er konstateret utilsvarende ift. dansk klinisk praksis, da en stor del af disse patienter ikke kan kategoriseres korrekt. Dette vil unægteligt efterlade patienter uden adgang til behandling, som ellers kunne have gavn af ribociclib baseret på NATALEE-studiets evidens.

5. **Tiltro til klinisk beslutningstagning:**
   Danske brystonkologer træffer behandlingsbeslutninger på baggrund af patientens individuelle risikofaktorer, komorbiditeter og præferencer – en proces, der allerede anvendes til vurdering af behovet for f.eks. kemoterapi. Ved at give adgang til ribociclib for non-monarchE-patienter understøttes denne skræddersyet behandling, der tilgodeser den enkelte patients behov snarere end en rigid, unuanceret populationsbaseret tilgang, der desværre vil lede til modstridende adgangsbetingelser for patienter med sammenlignelige risici på tværs af monarchE- og non-monarchE-subpopulationerne.

Opfordring til Medicinrådet:
Vi anbefaler, at Medicinrådet foretager en omkostningseffektivitetsanalyse for den samlede ITT-population og alternativt for non-monarchE-population, som kan afgøre, om ribociclib bør tilbydes bredere. Hvis ribociclib vurderes som omkostningseffektiv, bør behandlingen være tilgængelig baseret på en fælles beslutningstagning mellem læge og patient, med hensyntagen til den enkeltes risiko og behandlingsmål.

Novartis finder det problematisk, hvis ribociclib ikke tilgængeliggøres for non-monarchE-patienter, da det overser nuancerne i risikoprofilen og de betydelige kliniske behov hos disse patienter. Den aktuelle dokumentation viser en statistisk signifikant forbedring af IDFS og DRFS med konsistent relativ risikoreduktion. Argumentet om datamodenhed bør suppleres med en klar forventning i forbedringer i absolut effekt over tid, baseret på akkumulerede opfølgninger i NATALEE-studiet. Dette kan med fordel modelleres på baggrund af den allerede indsendte CUA-model.

Vi håber, at Medicinrådet vil tage disse overvejelser med i Medicinrådets endelige beslutning og dermed facilitere mere retfærdig adgang til ribociclib, der afspejler evidensen og patienternes behov.

Med venlig hilsen,
Novartis Healthcare A/S

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07.08.2025

DBS/MBA

Forhandlingsnotat

Dato for behandling i Medicinrådet	03.09.2025
Leverandør	Novartis
Lægemiddel	Kisqali (ribociclib)
Ansøgt indikation	Kisqali (ribociclib) i kombination med en aromatasehæmmer til adjuverende behandling af tidlig ER+/HER2-negativ brystkræft.
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende aftalepris på Kisqali (ribociclib):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Nuværende rabat ift. AIP
Kisqali	200 mg (21 stk.)	10.327,54	[redacted]	[redacted]
Kisqali	200 mg (42 stk.)	15.537,49	[redacted]	[redacted]
Kisqali	200 mg (63 stk.)	22.295,76	[redacted]	[redacted]

Aftaleforhold

Kisqali er en del af et udbud med de øvrige CDK 4/6-hæmmere: Verzenios (abemaciclib) og Ibrance (palbociclib). Amgros har en aftale med leverandøren, som gælder til den 31.03.2026. Aftalen kan ikke forlænges.

[redacted]

Konkurrencesituationen

Verzenios blev anbefalet af Medicinrådet til samme indikation i februar 2025.

Derudover er Kisqali og Verzenios ligestillet under 'Anvend' i behandlingsvejledningen vedrørende CDK4/6-hæmmere til ER+/HER2- lokalt fremskreden eller metastatisk brystkræft.

Tabel 2 viser sammenligningen af lægemiddeludgifter mellem Kisqali og Verzenios.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Kisqali	200 mg (63 stk.)	600 mg dagligt i 21 dage med en uges pause i cyklus a 28 dage.	[redacted]	[redacted]
Kisqali	200 mg (63 stk.)	Dosisjusteret RDI (dosisintensiteten) 83,4%	[redacted]	[redacted]
Verzenios	150 mg (56 stk.)	300 mg (2 x 150 mg) dagligt	[redacted]	[redacted]

* RDI (dosisintensiteten) fra Medicinrådets vurdering.

Status fra andre lande

Tabel 2: Status fra andre lande

Land	Status	Link
Norge	Under Vurdering	Link til vurderingen
England	Anbefalet	Link til vurderingen

Opsummering

[redacted]

Kisqali (ribociclib) for adjuvant treatment of patients with HR-positive, HER2-negative early breast cancer (eBC), irrespective of nodal status, at high risk of recurrence

Submitted by Novartis: 24th of April 2025

Resubmitted by Novartis: 21st of May 2025

Resubmitted by Novartis: 3rd of June 2025

Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information

Contact information

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Abbreviations

Abbreviation	Full term
aBC	Advanced breast cancer
AE	Adverse event
AI	Aromatase inhibitor
BC	Breast cancer
CDK4/6	Cyclin-dependent kinase 4/6
CT	Chemotherapy
eBC	Early breast cancer
DBCG	Danish Breast Cancer Group
DCO	Data cut-off
DDFS	Distant disease-free survival
DMC	Danish Medicines Council
DR	Distant recurrence
DRFS	Distant recurrence-free survival
EMA	European Medicines Agency
ER	Estrogen receptor
ET	Endocrine Therapy
EORTC-QLQ-30	European Organization for Research and Treatment of Cancer-Quality of Life questionnaire-30
EQ-5D-5L	EuroQol-5 Dimensions-5 Levels
EU	European Union
FDA	Food and Drug Administration
GLM	General linear model
HER2	Human epidermal growth factor receptor 2
HER2+	HER2 positive
HER2−	HER2 negative
HR	Hormone receptor
HR+	HR positive
HR−	HR negative
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICD	International Classification of Diseases
iDFS	Invasive disease-free survival
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
ISH	in situ hybridization
ITT	Intention-to-treat

LHRH	Luteinizing hormone-releasing hormone
LRRFS	Loco-regional recurrence-free survival
LY	Life-years
mBC	Metastatic breast cancer
NICE	National institute for health and care excellence
NMR	Non-metastatic recurrence
OFS	Ovarian function suppression
pALN	Pathologic auxiliary lymph node
PFS	Progression-free survivial
PPP	Pharmacy purchase price
pTNM	Pathologic TNM
QIC	Quasilikelihood independence criterion
PR	Progesterone receptor
PRO	Patient reported outcome
RFS	Recurrence-free survival
SAE	Serious adverse event
SEER	Surveillance, Epidemiology, and End Results
SERM	Selective ER modulators
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SPM	Second Primary Malignancy
STEEP	Standardized Definitions for Efficacy End Points
TAM	Tamoxifen
TNBC	Triple negative breast cancer
TNM	Tumor, node, metastases
TTD	Time-to-treatment discontinuation or death
VAS	Visual analog scale

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Kisqali
Generic name	Ribociclib (RIB)
Therapeutic indication as defined by EMA	Kisqali in combination with an aromatase inhibitor is indicated for the adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer at high risk of recurrence (see section 5.1 for selection criteria).

Overview of the medicine	
	In pre- or perimenopausal women, or in men, the aromatase inhibitor should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist
Marketing authorization holder in Denmark	Novartis Healthcare A/S
ATC code	L01EF02
Combination therapy and/or co-medication	Kisqali is given in adjuvant setting in combination with an aromatase inhibitor (AI), and if patients are pre-, perimenopausal or men the AI should be combined with an LHRH-agonist
Date of EC approval	27th of November 2024
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	Kisqali is indicated for the treatment of women with HR-positive, HER2-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy (ET)
Other indications that have been evaluated by the DMC (yes/no)	Yes, Kisqali has been recommended in the standard HTA procedure by the DMC for the treatment of metastatic HR+/HER- breast cancer on the 23rd of April 2018 and 25th September 2019
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? No Is the product suitable for a joint Nordic assessment? No If no, why not? Current treatment practice for high-risk patients with HR+/HER- EBC is different across the Nordic countries. There are some different practices in terms of local chemotherapy, radiation and surgical treatment regimens. Kisqali is already approved an in use for eBC in Sweden.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	The following pack sizes are available: Packs containing 21, 42 or 63 film-coated tablets Kisqali packs containing 63 tablets are intended for use by metastatic patients taking ribociclib daily dose of 600 mg (3 tablets once daily). Kisqali packs containing 42 tablets are intended for use by patients taking ribociclib full daily dose of 400 mg (2 tablets once daily). Kisqali packs containing 21 tablets are intended for use by patients taking the reduced ribociclib daily dose of 200 mg (1 tablet once daily).

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Kisqali in combination with an aromatase inhibitor is indicated for the adjuvant treatment of patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence (see section 5.1 for selection criteria). In pre- or perimenopausal women, or in men, the aromatase inhibitor should be combined with a LHRH agonist.
Dosage regiment and administration	Patients start on ribociclib full daily dose of 400 mg (2 tablets once daily). Ribociclib is given at a dose of 400 mg per day for 3 weeks, followed by 1 week off, for 3 years. The 3-year treatment duration of ribociclib in the NATALEE trial is intended to maximize on-target exposure of circulating tumor cells or dormant micro metastatic disease to ribociclib, thereby preventing recurrences even after stopping ribociclib treatment. The full dose has been reduced from 600 mg, used in the advanced metastatic, to 400 mg to optimize the balance between efficacy and safety in the eBC setting. The SmPC holds a recommended dose modification guideline (see section 3.4) (1).
Choice of comparator	Clinical practice is driven by the current DBCG treatment guidelines (2). The Danish breast cancer group (DBCG) guideline recommends almost all HR+ eBC patients receive an adjuvant ET regimen depending on age and TN staging. Premenopausal women and men are predominantly offered tamoxifen (TAM), with or without ovarian suppression with goserelin. Postmenopausal women are recommended treatment with an AI (2).
Prognosis with current treatment (comparator)	The patients with eBC in scope for ribociclib have an unfavorable prognosis based on local RWE (DBCG eBC registry), [redacted] dying at the 7-year landmark analysis (3). The data conforms with other international data and shows patients continue to experience recurrence at an almost constant rate for a 20-year period (4).
Type of evidence for the clinical evaluation	Head-to-head data from NATALEE, a phase-III trial: A Trial to Evaluate Efficacy and Safety of Ribociclib With Endocrine Therapy as Adjuvant Treatment in Patients With HR+/HER2- Early Breast Cancer. NCT03701334. Three separate data-cuts have been presented and reported, 1) a second-interim analysis with 3-year landmark data with a 27.7 months of median FU (5), 2) final iDFS data with a median FU of 33.3 months (6). 4-year landmark data with a median FU of 44.2 months was presented by Fasching et al. at ESMO (7, 8). The 4-year data-cut is used for the clinical evaluation and in health economic evaluation and relies mostly on data-on file (9), set to be published before the DMC recommendation. PRO data rely on data-cut with 27.7 months follow-up (10), as more recent data-cuts only included updates to efficacy and safety.

Summary	
	If not otherwise stated, the data presented is from the 4-year landmark data-cut.
Most important efficacy endpoints (Difference/gain compared to comparator)	Main efficacy outcomes for the application (presented as 4-year landmark, ITT-analysis, RIB + ET vs. ET alone): Invasive Disease-Free Survival (IDFS), 4-year rate: 88.5% vs. 83.6%, ARR: 4.9%, HR: 0.715 (0.609-0.840), p <0.0001 Distant disease-free survival (DDFS), 4-year rate: 89.4% vs. 84.9%, ARR: 4.5%, HR: 0.715 (0.604–0.847), p <0.0001 [redacted] Overall Survival (OS), 4-year rate: 95.0% vs. 94.2%, ARR: 0.8%, HR: 0.827 (0.636–1.074), p = 0.0766.
Most important serious adverse events for the intervention and comparator	In the RIB + ET arm 14.8% compared to 10.9% in the ET only arm experienced a SAE. However, all SAEs had an incidence of <1% in both arms and in total, and no SAE in particular stands out.
Impact on health-related quality of life	Clinical documentation: The EORTC-QLQ-30 and VAS scores were generally similar between the two treatment arms throughout the study, with no meaningful differences at any post-baseline timepoint through to the EOT. This supports that RIB + ET has good tolerability in the adjuvant setting.
Type of economic analysis that is submitted	The economic model used for the comparison versus ET will be a cost-utility analysis in the form of a non-homogenous Markov cohort model, including time-dependent transition matrices. LYs and time on treatment in distant relapse health states were modeled via a partitioned survival framework using progression-free survival (PFS), TTD (time-to-treatment discontinuation or death), and OS data from the MONALEESA-2 and MONALESSA-3 trials of ribociclib. Extrapolations of PFS were used to calculate the proportions of patients in PFS by time since distant relapse. Proportions of patients in post-progression survival were calculated as the difference between extrapolated OS and PFS curves. LYs were then calculated based on expected PFS and PPS and time on treatment was calculated based on extrapolated TTD. QALYs in distant relapse states were calculated by multiplying expected pre- and post-progression LYs by health state utilities for PFS and PPS, respectively.
Data sources used to model the clinical effects	Head-to-head data from NATALEE
Data sources used to model the health-related quality of life	HRQoL measured with EQ-5D-5L in the NATALEE trial. April 29, 2024, DCO. Danish population weights are used.
Life years gained (discounted)	[redacted]
QALYs gained (discounted)	[redacted]
Incremental costs (discounted)	[redacted]

Summary	
ICER (DKK/QALY)	[redacted]
Uncertainty associated with the ICER estimate	The model assumptions that hold the greatest impact on the overall results are the efficacy difference in iDFS, treatment effect waning, utility assumptions, and the type of iDFS event.
Number of eligible patients in Denmark	Incidence: 537 patients/year Prevalence: Not known in target population and of limited relevance, as only patients initiated on ET within 12 months will be eligible if following the treatment practice in NATALEE. This has been accounted for in the budget impact.
Budget impact (in year 5)	[redacted]

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

Breast cancer (BC) is the most common cancer among women in Denmark, with 5,412 new cases reported in 2023 — a 4.9% increase from the previous year (11). The lifetime risk of breast cancer before the age of 80 is 11.8%, meaning that 1 in 8 Danish women will develop BC before turning 80 (12).

BC is classified according to the cell type from which the tumor arises and is described in terms of estrogen receptor (ER) status, progesterone receptor (PR) status, and HER2 status. Collectively, ER and PR may be referred to as hormone receptors (HR). The HR and HER2 status may be denoted as either positive or negative. HR+/HER2- disease, meaning that the cancer cells express ER but not HER2, is the most common subtype, representing approximately 70% of all BC cases(13). 3,300 patients are diagnosed annually with ER+/HER2- breast cancer in Denmark (14).

EBC can be defined as not having spread beyond the breast tissue or nearby lymph nodes and generally includes ductal carcinoma in situ (Stage 0) and Stages I–IIIA, but may also be defined as invasive breast cancer stages I–IIIC, excluding Stage 0 carcinoma (15). Anatomical staging of breast cancer is based on the size and extent of the breast tumor (T), the extent of regional lymph node involvement (N), and the presence/absence of distant metastases (M) (16). These features are assigned individual scores, which are then combined to identify the stage (Stage 0-IV) (17).

Most HR+/HER2- BC cases are diagnosed at early stages. However (18), recurrence remains a significant concern and can transform a curable condition into something that is difficult to treat, micro-metastases undetectable via imaging and ultimately terminal metastatic disease (19).

Studies have shown that approximately one-third of patients with stage II disease and half of those with stage III will experience recurrence within 20 years after initial diagnosis (20-23). Notably, this risk persists over time and is irrespective of nodal involvement (Table 1). Risk of recurrence is highest during the first 5 years after diagnosis, but >50% of patients experience late recurrences (≥5 years from diagnosis; Table 1) (4, 21-23). Thus, the prevention of both early and late recurrences are equally important considerations when making adjuvant treatment recommendations for patients with HR+/HER2- eBC (24).

Table 1 Association between pathological nodal status and the risk of distant recurrence during years 0 to 20, according to tumor stage.

Distant recurrence rate (%)	Tumor stage and nodal status (TNM)					
	T1N0	T1N1	T1N2+	T2N0	T1N1	T2N2+
5-year	4	7	17	9	14	25
10-year	8	14	30	16	24	41
15-year	13	20	39	23	31	49
20-year	18	27	46	29	37	57

Note: Reproduction of data presented by Pan et al (4). Note: 74,194 women with T1/T2 N0-9 ER+ disease entered at year 0 and scheduled 5 years of ET.

Typical 5-year recurrence/survival rates are indicative of total treatment effect for most cancer types. These are, however, not sufficient for HR+/HER2- eBC where the cumulative risk of recurrence increases steadily over time (4). In HR+/HER2- eBC, 10–15-year recurrence and survival rates provide a clearer picture of the nature of the cancer. Therefore, clinical trials in adjuvant setting are subject to a certain dilemma on striking the balance between awaiting full information on recurrence and survival and on the other hand accepting a certain degree of uncertainty, as it is not practical or ethical to await full information on recurrence and survival on new interventions. Prior approvals of ET/CT in adjuvant setting have been adopted without initial data on overall survival data based on disease-free survival (DFS) or similar measurements and with follow-up data close to what is provided in this dossier (25). These should be considered when establishing a decision threshold of data maturity and surrogacy endpoints.

While standard adjuvant ET has improved outcomes, a substantial proportion of stage II and III HR+/HER2- eBC patients experience disease recurrence. A follow-up analysis to Pan et al. study (Table 1) was recently published. While increasing nodal status is associated with increased recurrence rates, patients with HR+ N0 disease have a meaningful risk of distant recurrence of 7.3% at 10 years. In the subset of patients with node-negative disease and additional risk-feature, such as larger tumors (T2N0), the 10-year risk of distant recurrence was 18.6%, more than double that of the overall N0 population. T2N1 had a similar risk of recurrence of 19.1% at 10 years (26). This highlights the necessity to look at the totality of the factors contributing to the patient's risk profile and not solely on nodal status, as N0 patients with additional high-risk features have a highly elevated risk

equal to that of N1 patients. Danish registry data, described in the section below, shows similar risk of recurrence between the high-risk N0 patients and N1 patients.

3.1.1 Danish registry data on Danish patient prognosis with the current treatment options

The following section presents data from the DBCG eBC registry on a Danish NATALEE cohort (3). The data is used to establish the local prognosis, treatment and baseline characteristics in patients, which would fulfill the inclusion criteria in the NATALEE trial, the pivotal trial of interest for this submission. More details about the registry, baseline characteristics and analysis (landmark and time-to event for iDFS, DDFS, DRFS and OS) can be found in Appendix K and section 3.2 below. Key high-level data is presented below.

DBCG extracted data from the DBCG eBC registry, a nationwide, clinical database on women diagnosed with primary invasive non-metastatic breast cancer (3, 27). Data on patients diagnosed 2014-2019 was extracted on a population that corresponds to the NATALEE population, with an estimated median follow-up on overall survival of 7 years and 2 months, and a median clinical follow-up of 6 years and 6 months. For baseline and treatment characteristics see Appendix K.

[redacted]

[redacted]

[redacted]

3.2 Patient population

The population of interest for this submission are HR+/HER- eBC patients with high risk of recurrence, irrespective of nodal status. Our definition of the high-risk population aligns with the patient population of the NATALEE trial, which is very similar to the patients selected in Danish NATALEE cohort from the DBCG registry (Appendix K), hereafter referred to as the DBCG cohort. This population is broader than monarchE (see Appendix M, Figure 58, for comparison). Briefly, NATALEE included all stage II and III patients with N1, N2 and N3, and for N0 all T3 and T4 were included, whereas T2 patients had to fulfill either grade 3 or grade 2 + high genomic risk or KI-67 ≥ 20% to be included.

The NATALEE trial (NCT03701334) evaluates ribociclib combined with endocrine therapy (ET) in the adjuvant treatment of patients with stage II and III HR+/HER2- early breast cancer (eBC). This trial includes a broader patient population at high risk of recurrence, extending eligibility to all node-positive patients. Unlike the monarchE trial, which focused on a restricted subset of N1-node-positive patients (N1 with Ki67>20% or T >5 cm or grade 3), the NATALEE trial addresses the unmet medical need among all high-risk patients. In addition to all node-positive patients, NATALEE also includes high-risk node-negative patients (T2 grade 3 or grade 2 disease with additional risk factors) who have limited options beyond ET and share a similar poor prognosis as N1-positive patients, as documented in DBCG registry data (Appendix K). Currently, the SENOMAC practice complicates the accurate identification of the full monarchE-eligible population, since axillary lymph node dissection has been replaced with local radiation (SENOMAC practice) for patients with 1-2 positive sentinel nodes. This means that a proportion of patients risk being under-staged and therefore not deemed eligible for CDK4/6i as per the monarchE trial. This is expressed to be a daily dilemma by several Danish physicians. If the full NATALEE population is approved, the SENOMAC practice will no longer pose a clinical dilemma, which is considered very positive according to several Danish physicians.

With consistent treatment effects observed across all subgroups, NATALEE demonstrates the importance of addressing the full intention-to-treat (ITT) population (6.1.4). Local real-world evidence presented in section 3.1 supports the need to expand treatment options for high-risk patients regardless of nodal status. Therefore, the full ITT population is the scope of the submitted analysis.

3.2.1 Incident patient population

The Danish incidence estimates are based on the DBCG cohort, using TNM-stage and high-risk criteria similar to NATALEE (Appendix K). Data from 2014-2019 and 2020-2022 demonstrates a stable incidence of new patients, averaging 1,033 patients per year in the first period and 1,023 per year in the second. The incidence rate is expected to remain stable from 2023 onwards.

The prevalent population in Denmark is largely irrelevant, as the patients previously diagnosed and already undergoing adjuvant treatment are generally outside the scope for adjuvant ribociclib treatment. However, in the NATALEE trial, patients who had initiated their ET within less than one year could commence adjuvant ribociclib. Thus, there is a

limited pool of patients diagnosed within the last year prior to a DMC recommendation who could start ribociclib.

Table 2 Incidence and prevalence in the past 5 years

Year	2020*	2021*	2022*	2023*	2024*
Incidence in Denmark	≈1,033	≈1,033	≈1,033	≈1,033	≈1,033
Prevalence in Denmark	NR	NR	NR	NR	NR

Astrix: *Numbers entered based on yearly averages in the periods 2020-2022 from DBCG registry.

Abbreviation: NR; Not relevant

3.2.2 Eligible patient population

Clinical practice

The DBCG eBC registry data indicates that approximately 6.6% of the incident population does not receive any ET. This may be attributed to patient preferences or end-of-life considerations. As a result, these patients are excluded from the scope for adjuvant ribociclib which is indicated only for patients receiving ET. Therefore, the eligible population is reduced from 1,023 to 955 patients.

Until recently, current DBCG guidelines in Denmark recommended TAM as the ET for all premenopausal and perimenopausal women who account for roughly 30% of the Danish HR+/HER- eBC patients (3, 28).

However, recent revisions of the DBCG guidelines, aimed at optimizing outcomes for premenopausal women, have resulted in a change to recommend AI over TAM for younger premenopausal women (2). This concerns all premenopausal women < 35 years of age and patients with high-risk features with an age of ≥ 35 years to < 40 years for whom the recommendation now favors exemestane (AI) + goserelin instead of TAM as the first-choice therapy. These changes have yet to be fully implemented in Danish clinical practice and are deemed to be a gradual transition. As mentioned, ribociclib is not to be given with TAM, and if ribociclib is approved and introduced in adjuvant setting, it is not as a base-case anticipated to change the future treatment practice or choice of ET therapy. As a conservative assumption we therefore lower the use of TAM from ≈ 30% of patients today to around ≈ 25% going forward which will reduce the eligible population further to 716 patients.

This will represent an upper theoretical limit for patients eligible for adjuvant ribociclib. However, the actual number of patients who will receive ribociclib is estimated to be much lower. This is due to the fact that current treatment practice in Denmark is driven by shared decision making, and especially for post-menopausal women it is focused on conservative treatment by restricting chemotherapy in adjuvant setting for patients with little or no excess overall mortality risk by using a prognostic score index (PSI-score) (2). The focus on shared decision making was also reiterated and taken into account in the estimation of the eligible patient population in the DMC's assessment of abemaciclib (28).

Shared decision making

According to the consulted clinical expert, patient age, expected lifespan, motivation, psychological and physical fragility will be considered before initiating treatment with CDK4/6 inhibitors in the adjuvant setting.

The actual number of patients eligible for ribociclib in the eBC setting will as a result be lower than the theoretical eligible pool of 716 patients. The clinical expert assumed that 75% of the eligible patients will be relevant for treatment based on a shared decision-making process. As an example, patients ≥ 70 years with comorbidities are deemed less likely to have a CDK4/6i added to their adjuvant treatment. Patients ≥ 70 years represent 30% of the incident patients and a high proportion is expected to have significant comorbidities. Similarly, a Belgian RWE analysis shows early implementation patterns for adjuvant treatments, showing that out of an estimated 840 eligible patients, only 311 (37%) initiated abemaciclib therapy during the first 10 months (29). This supports that the full eligible population will likely not start treatment in clinical practice, and an aggressive assumption would be that around 75% of the eligible population of 716 patients will be relevant for treatment in a real-world setting in Denmark, i.e. 537 patients.

Recall of eligible patients already diagnosed and treated with ET

The consulted clinical expert expects that patients initiated on ET within one year of the recommendation of ribociclib will be recalled for a clinical assessment to determine if ribociclib should be initiated. This practice would conform with the practice in NATALEE, where patients were allowed to start ribociclib if initiated on ET within 1 year. The patient population will not be a full year of eligible patients, because abemaciclib will have been recommended 6 months earlier in an overlapping subset of patients. Although the impact of this is considered uncertain, additional patients have been added to year 1 corresponding to the half of the yearly eligible patient count Table 4.

Table 3 Estimated number of patients eligible for ribociclib

	Proportion (%)	Number of patients per year
NATALEE population (TNM + risk factors)	100	1,023
Receiving ET	93.4	955
Receiving AI (minus TAM)	75	716
Shared decision making	75	537

Table 4 Estimated number of patients eligible for treatment

Year	2025	2026	2027	2028	2029
Eligible patients	≈805*	≈537	≈537	≈537	≈537

*Higher, as a recall of patients from one year prior to the reimbursement is anticipated and half of these are expected to be started on adjuvant ribociclib.

3.3 Current treatment options

According to DBCG's yearly report from their quality database almost all Danish patients with eBC HR+/HER2-(around 85-90%) undergo surgical treatment and possibly radiotherapy (30). Based on the DBCG guideline additional medical treatment such as chemotherapy (CT) and ET is recommended if the mortality rate without treatment is estimated not to be age-equivalent and the risk of recurrence is more than 10% after 10 years. For patients with HR+/HER2- breast cancer, where there is an indication for CT and who have T1-2, N0-1, M0 disease, 6 cycles of CT are recommended. The recommended regimens are taxane and anthracycline given sequentially or 6 cycles of docetaxel and cyclophosphamide. If ET is indicated, treatment duration as well as type of ET is planned based on age, prognosis, menopausal status, tumor subtype, and any comorbidities (31).

Pre- and perimenopausal patients are recommended adjuvant treatment with exemestane or TAM for 5 years. The adjuvant ET can be extended for an additional 5 years, if the patient has lymph node-positive breast cancer. Patients diagnosed and treated when pre- and perimenopausal with lymph node-positive breast cancer, who are recurrence-free and become postmenopausal after 5 years of TAM, should be recommended extended treatment with AI for 5 years. Premenopausal women aged ≥ 35 and < 40 years, operated for early HR+ breast cancer with either a tumor > 2 cm or malignancy grade 3, alternatively lymph node-positive disease, can after completing CT be recommended 5 years of adjuvant exemestane and goserelin, supplemented with 3 years of zoledronic acid. Premenopausal women ≤ 35 years with an estimated high risk of recurrence, who have undergone CT, are recommended monthly treatment with a gonadotropin-releasing hormone (GnRH) agonist for 2 years in addition to TAM. For a full overview refer to the DBCG guideline (31).

Postmenopausal women are recommended 5 years of treatment with an AI. Additional 6-8 cycles of CT treatment (possibly neoadjuvant, possibly dose-dense) is recommended for patients with PSI ≥ 3. All postmenopausal women are offered 3 years of zoledronic acid in addition to ET. For a full overview refer to the DBCG guideline (31).

For patients corresponding to the NATALEE patient population, adjuvant ET is recommended post-operatively and after possible radiotherapy and CT. This applies to patients with ER-positive (≥ 10%) tumor and/or 1-9% ER-positive tumor with luminal A/B subtype (for example, by PAM50).

The DMC recently recommended abemaciclib for HR+/HER- lymph node positive patients with a high risk of recurrence. Consequently, the full eBC indication of ribociclib is comprised by an overlapping patient population, which are eligible for abemaciclib, and a non-overlapping population which is unique for NATALEE and only eligible for ribociclib. The current treatment options therefore differ between these two populations, with the overlapping population (monarchE) treated with a combination of ET, CT as stated above and in addition to this abemaciclib, whereas the non-overlapping is not eligible for abemaciclib and treated with ET and CT as stated above. The eligibility criteria for these two patient populations are available in Figure 58. The non-overlapping population of NATALEE consists of N0 patients with high-risk features (such as grade III and large tumors)

and N1 patients without high-risk features excluded from monarchE. Separate results for the overlapping and non-overlapping subgroups are provided in Appendix L.2.

3.4 The intervention

Overview of intervention	
Therapeutic indication relevant for the assessment	Kisqali in combination with an aromatase inhibitor is indicated for the adjuvant treatment of patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence (see section 5.1 for selection criteria). In pre- or perimenopausal women, or in men, the aromatase inhibitor should be combined with a LHRH agonist. Section 5.1 selection criteria: Anatomic stage group IIB-III, or Anatomic stage group IIA that is either: Node positive or node negative, with: Histologic grade 3, or Histologic grade 2, with any of the following criteria: Ki67 ≥20% High risk by gene signature testing Premenopausal women, and men, also received goserelin. Applying TNM criteria, NATALEE included patients with any lymph node involvement (excluding microscopic nodal involvement), or if no nodal involvement either tumor size >5 cm, or tumor size 2-5 cm with either grade 2 (and high genomic risk or Ki67 ≥20%) or grade 3.
Method of administration	Film-coated tablets, taken orally
Dosing	Patients are started on ribociclib full daily dose of 400 mg (2 tablets once daily). Ribociclib is given at a dose of 400 mg per day for 3 weeks, followed by 1 week off, for 3 years. The full dose has been reduced from 600 mg used in the advanced metastatic to 400 mg to optimize the balance between efficacy and safety in the eBC setting (see section 6.1.1.1 for dosing rationale). The SmPC holds a recommended dose modification guideline, wherein certain adverse events (i.e. liver function tests, QT-prolongation and neutropenia) result in either dose reduction to 200 mg (1 tablet once daily) or discontinuation (1).
Dosing in the health economic model (including relative dose intensity)	Same as above, relative dosing intensity: 83.4 %.
Should the medicine be administered with other medicines?	Ribociclib is added to existing adjuvant treatment consisting of an AI and in pre- or perimenopausal women and in men a LHRH-agonist (goserelin) should be added.
Treatment duration / criteria for end of treatment	3-years of adjuvant ribociclib treatment or until treatment progression (see section 6.1.1.1 for treatment duration rationale). Dose reductions and discontinuation should be performed as per the SmPC (1). Discontinuation of ribociclib is

Overview of intervention	
	mainly indicated because of hepatobiliary toxicity (grade 3 and 4) and QT-prolongation.
Necessary monitoring, both during administration and during the treatment period	Liver function tests (LFTs) and complete blood counts (CBC) should be performed before initiating treatment with ribociclib. After initiating treatment LFTs and CBC should be monitored every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, then as clinically indicated. If grade ≥ 2 abnormalities are noted, more frequent monitoring is recommended. ECG should be assessed before initiating treatment with ribociclib in all patients. After initiating treatment, ECG should be repeated at approximately day 14 of the first cycle, then as clinically indicated.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	Patient selection for treatment with ribociclib is based on the tumor expression of HR and HER2 which should be assessed by a CE-marked *in vitro* diagnostic medical device with the corresponding intended purpose. However, no additional tests are needed, as patients are already tested in Danish clinical practice for HR and HER2 expression.
Package size(s)	The following pack sizes are available: Packs containing 21, 42 or 63 film-coated tablets Kisqali packs containing 63 tablets are intended for use by patients taking the ribociclib daily dose of 600 mg (3 tablets once daily). Only relevant for metastatic patients. Kisqali packs containing 42 tablets are intended for use by patients taking ribociclib full daily dose of 400 mg (2 tablets once daily). Kisqali packs containing 21 tablets are intended for use by patients taking the reduced ribociclib daily dose of 200 mg (1 tablet once daily).

3.4.1 The intervention in relation to Danish clinical practice

Ribociclib is expected to be used according to the EMA label. Ribociclib will therefore be used together with existing ET and not cause any changes to the eBC treatment pathway, i.e. no treatments will be replaced or displaced. Kisqali is to be used in combination with an AI indicated for the adjuvant treatment of patients with HR+/HER2- eBC at high risk of recurrence. In pre- or perimenopausal women, or in men, the AI should be combined with a LHRH-agonist.

There are no clinical trials to support any change in the existing treatment pathway for advanced or metastatic treatment because of the introduction of ribociclib in the eBC treatment pathway. However, according to the clinical expert consulted, a likely scenario for the future treatment practice will depend on the interval after discontinuation of CDK4/6i + ET treatment in adjuvant setting until disease recurrence. If recurrences occur during or within < 12 months of stopping CDK4/6i in eBC, the recommended practice could for example be to continue with CT in the aBC setting. If the recurrences occur more than ≥ 12 months after stopping CDK4/6 standard of care could be treatment with another CDK4/6 inhibitor combined with fulvestrant. We expect upcoming guidelines from DBCG

or DMC will address how to handle re-treatment of patients previously treated with CDK4/6 in eBC setting.

3.5 Choice of comparator(s)

Ribociclib is expected to be used in combination with AIs (anastrozole, exemestane or letrozole) in patients with HR+/HER2- eBC at high risk of recurrence. Ribociclib is not to be used with TAM. Currently, there is no DMC guideline for high-risk HR+/HER2- eBC, and clinical practice is driven by the current DBCG treatment guidelines (2). The DBCG guideline recommends that all HR+ eBC patients receive adjuvant ET according to menopausal status and gender as specified in section 3.3 (2).

According to the DBCG guideline premenopausal women and men are predominantly offered TAM, with or without ovarian suppression with goserelin. A recent revision as of September 2024 of the DBCG guideline to focus on optimizing outcomes for premenopausal women have resulted in a change to recommend AI over TAM for selected younger premenopausal women (< 40 years) to reduce their risk of recurrence. These changes are now being implemented in Danish clinical practice, however, most pre- and perimenopausal women in Denmark will continue to receive TAM and will therefore not be in scope for ribociclib in eBC in our base-case.

Postmenopausal women are recommended treatment with an AI (letrozole, anastrozole or exemestane) or alternatively TAM, if an AI is not tolerated or contraindicated. Patients at high-risk of recurrence should be offered extended adjuvant ET from five to ten years (2).

Patients in the NATALEE trial received the following ET:

- Anastrozole: ≈ 31.5%
- Letrozole: ≈ 68.5%

The proportional split between ETs differs between NATALEE and Danish clinical practice, because ribociclib is not recommended to be used with TAM, and only NSAI (anastrozole or letrozole) were used in the trial. This is not deemed problematic for the transferability of the results to the Danish clinical practice, as exemestane and NSAI have similar efficacy in eBC and AIs have been proven more efficacious than TAM (32, 33). Consequently, the unadjusted results of the NATALEE trial are deemed conservative estimates (underestimating) of the relative and absolute efficacy compared to the ET regimen used in Danish clinical practice. The base-case scenario in the health economic analysis will use the ET split used in the NATALEE ET only comparator-arm, and a scenario analysis, where the comparator-arm is adjusted to include TAM and exemestane according to Danish clinical practice. However, this scenario analysis uses hazard ratios (HR) not from the direct head-to-head trial (NATALEE) but instead rely on indirect treatment comparisons (ITC) from the literature and is therefore considered less robust.

The proportion split used in Danish clinical practice, is given below based on the DMC assessment of abemaciclib (28). Compared to the DMC's preferred treatment split (28),

we have adjusted the expected use of exemestane from 5% to 10%, and TAM from 30% to 25%.

- Anastrozole: ≈ 5%
- Exemestane: ≈ 10%
- Letrozole: ≈ 60%
- Tamoxifen: ≈ 25%

This reflects the latest changes in treatment practice for premenopausal women with an increased focus on use of exemestane over TAM. The differences between the clinical trial and Danish clinical practice are likely to result in conservative estimate of efficacy as the NSAI backbone included in NATALEE are considered clinical equivalent to exemestane and superior to TAM.

Detailed information on the comparators used in the base-case is given in tables below. Tamoxifen is not used as a comparator in the base-case modelling, as patients receiving TAM are not eligible for ribociclib. TAM would only be considered a valid comparator, if the introduction of ribociclib in adjuvant setting changed the current treatment practice for ET, so that patients currently receiving TAM would instead receive an AI to become eligible for ribociclib. In a recent Danish advisory board conducted by Novartis, the advisors informed Novartis, that they would strongly consider changing the ET backbone for patients currently receiving TAM if ribociclib was to be recommended by the DMC. A scenario analysis where TAM is included in the comparator-arm is therefore presented. This results in a significant lower ICER compared to the base-case and the result aligns closer to the ICER in the DMC's assessment of abemaciclib where TAM is included. This is a result of having an inferior treatment mix (TAM) in the ET-only arm yielding a higher incremental efficacy gain for the intervention (abemaciclib/ ribociclib). This also highlights one of the pitfalls of comparing the efficacy or ICER estimates between ribociclib and abemaciclib, as both the comparator and target population are fundamentally different (Appendix M).

Table 5 Description of Letrozole

Subject	Letrozole
Generic name	Letrozole
ATC code	L02BG04
Mechanism of action	Aromatase inhibitor blocking the synthesis of estrogen, thereby inhibiting the stimulation of estrogen on HR-positive breast cancer cells and tumor growth
Method of administration	Oral, Tablets/Film-Coated Tablets
Dosing	2.5 mg orally, once daily
Dosing in the health economic model (including relative dose intensity)	2.5 mg orally, once daily, relative dose intensity: 99.03 % in RIB + ET arm, and 99.18% in the ET only arm
Should the medicine be administered with other medicines?	No

Subject	Letrozole
Treatment duration/ criteria for end of treatment	5 years, unless the patient experiences disease progression or unacceptable toxicity
Need for diagnostics or other tests (i.e. companion diagnostics)	The tumor cells most be confirmed to be HR+ by valid examination by a pathologist
Package size(s)	Letrozole" Abacus medicine" 2.5mg, 30 pcs. coated tablets (blister) Letrozole "Accord" 2.5mg, 100 pcs. coated tablets (blister) Femar® 2.5mg, 100 pcs. coated tablets (blister) Letrozole "2care4" 2.5mg, 30 pcs. coated tablets (blister) Letrozole "Medical Valley" 2.5mg, 30 pcs. and 100 pcs. coated tablets (blister) Letrozole "Stada" 2.5mg, 100 pcs. coated tablets (blister)

Table 6 Description of Anastrozole

Subject	Anastrozole
Generic name	Anastrozole
ATC code	L02BG03
Mechanism of action	Aromatase inhibitor blocking the synthesis of estrogen, thereby inhibiting the stimulation of estrogen on HR-positive breast cancer cells and tumor growth
Method of administration	Oral, Tablets/Film-Coated Tablets
Dosing	1 mg orally, once daily
Dosing in the health economic model (including relative dose intensity)	1 mg orally, once daily, relative dosing intensity: 99.03 % in RIB + ET arm, and 99.18% in the ET only arm
Should the medicine be administered with other medicines?	No
Treatment duration/ criteria for end of treatment	5 years, unless the patient experience disease progression or unacceptable toxicity
Need for diagnostics or other tests (i.e. companion diagnostics)	The tumor cells most be confirmed to be HR+ by valid examination by a pathologist
Package size(s)	Anastelb 1mg, 100 pcs. coated tablets (blister) Anastrozole "Sandoz" 1mg, 100 pcs. coated tablets (blister) Anastrozole "Accord" 1mg, 98 pcs. coated tablets (blister) Anastrozole "Medical Valley" 1mg, 98 pcs. And 100 pcs. coated tablets (blister) Armidex® 1mg, 98 pcs. coated tablets (blister)

3.6 Cost-effectiveness of the comparators

The comparator-arm consist of different ETs that are all affordable generic medicines which are considered well-established in Danish clinical practice for decades. All have

several high-quality RCT documenting efficacy and are considered highly cost-effective by any standards. None of them have been evaluated by the DMC, as the medicines were approved decades ago. Based on the above, we find the criteria are fulfilled to avoid a supplementary analysis against a comparator that could reasonably be assumed to be cost-effective (i.e. placebo) and no supplemental analysis is needed (Section 2.4.2 of the Methods guideline).

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

The primary endpoint of the NATALEE trial is iDFS according to Standardized Definitions for Efficacy End Points (STEEP) criteria as assessed by the investigator. The STEEP definition of iDFS includes invasive, ipsilateral breast tumor recurrence, local or regional invasive recurrence, distant recurrence, death (from BC, non-BC, or unknown cause), invasive, contralateral BC, or second primary invasive cancer (non-BC). Although OS is a key endpoint for assessing the efficacy of cancer treatments, extensive follow-up times are needed to observe enough events, particularly when assessing treatments in the adjuvant setting. Therefore, iDFS has been adopted as a clinically meaningful and timely measure of efficacy in the eBC trials, with recent analysis showing its robustness as a validated surrogate endpoint for OS (34, 35).

Secondary endpoints include DDFS and OS and in addition DRFS (exploratory endpoint) have been added, as some clinicians prefer this endpoint. Herein, we only provide evidence for the surrogacy of the primary endpoint iDFS to OS. No claims for surrogacy for DDFS/DRFS are made, as no specific analysis has been conducted to validate DDFS/DRFS. However, the individual type of events measured in DDFS/DRFS are all included in the iDFS definition (Table 8). DRFS was conducted as an exploratory efficacy analysis and is included here, as it was of particular interest to the DMC in the assessment of abemaciclib, although it is very similar to the secondary endpoint, DDFS (Table 8)(28).

For iDFS, we provide extensive documentation for its validity as a robust surrogate outcome for OS (see section below). Furthermore, as documented below (Table 24), more than ≥ 70% of the events accounted for by iDFS would also qualify as a DDFS event. The events covered by DDFS are death, distant recurrence of BC, and second primary invasive cancer. Distant recurrences are by consensus considered incurable disease by clinicians. Based on the overwhelming similarity between iDFS and DDFS/DRFS, the robust validity of iDFS as a surrogate for OS, and the fact that distant recurrences are incurable, we argue that a high degree of correlation between the DDFS/DRFS endpoint and OS is expected.

All efficacy outcomes reported pertain to the 4-year landmark analysis conducted with the 29 April 2024 data cut-off (DCO) with a median follow-up time for iDFS of 44.2 months.

Table 7 Efficacy outcome measures relevant for the application

Outcome measure	Time point	Definition	How was the measure investigated/method of data collection
iDFS Primary	4-year landmark analysis, median FU: 44.2 mo.	Composite surrogate endpoint for OS: Invasive, ipsilateral breast tumor recurrence local or regional invasive recurrence Distant recurrence death attributable to any cause invasive, contralateral BC or second primary invasive cancer (non-BC).	STEEP criteria, investigator assessed and measured from the date of randomization to the first occurrence of any of the relevant events (see definition). Patients who do not have an iDFS event will be censored at the last recurrence assessment on or prior to the data cut-off.
DDFS Secondary	4-year landmark analysis, median FU: 44.2 mo.	Composite endpoint: - Distant recurrence - Death (any cause) - Second primary non-breast invasive cancer (excluding basal and squamous cell carcinomas of the skin).	STEEP criteria, investigator assessed and measured from the date of randomization to the first occurrence of any of the relevant events (see definition). Patients who do not have a DDFS event will be censored at the last recurrence assessment on or prior to the data cut-off.
DRFS Exploratory	4-year landmark analysis, median FU: 44.2 mo.	Composite endpoint: - Distant recurrence - Death (any cause)	See above
OS Secondary	4-year landmark analysis, median FU: 44.2 mo.	OS is defined as the time from randomization to death from any cause.	See above, Investigator assessed

Statistical methods and reporting for primary and secondary endpoints

The primary efficacy variable, iDFS, was analyzed using a Lan-DeMets (O'Brien-Fleming) alpha spending function and a non-binding Lan-DeMets (O'Brien-Fleming) beta spending function based on the data observed in the ITT up to the cut-off date, according to the treatment arm and strata assigned at randomization. The analysis to test this hypothesis consisted of a stratified log-rank test at an overall one-sided 2.5% level of significance based on the randomization stratification factors. The survival distribution of iDFS was estimated using the Kaplan-Meier method. The results were plotted graphically by

treatment arm. The iDFS rate with 95% confidence intervals was presented for each of the two treatment arms. A stratified Cox proportional regression was used to estimate the HR of iDFS along with 95% confidence interval using the same strata information as the primary efficacy comparison. P-values for 4-year landmark data are reported as 1-sided p-values 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. An approach identical to the above was used for the other efficacy outcomes (OS, DDFS and DRFS).

Overview of efficacy outcomes included

Table 8 Overview of events included in the efficacy outcomes included in submission

Events included in the endpoint	OS	iDFS	DDFS	DRFS
Death from BC	X	X	X	X
Death From Non-BC cause	X	X	X	X
Death From Unknown cause	X	X	X	X
Invasive ipsilateral BC recurrence		X		
Local/regional invasive recurrence		X		
Distant recurrence		X	X	X
Invasive contralateral BC		X		
Ipsilateral DCIS				
Contralateral DCIS				
Second primary invasive cancer (non-breast)		X	X	

Validity of outcomes

Invasive disease free-survival - iDFS:

iDFS was chosen as the primary endpoint in NATALEE, as it is considered an appropriate and adequate endpoint for this trial to reflect the efficacy of ribociclib in the adjuvant setting. Recently the DMC has recommended another CDK4/6 inhibitor, abemaciclib, which rely on the same definition of iDFS as their primary endpoint and for the health economic modelling (28). A standardized definition of iDFS was used in NATALEE, as per the STEEP criteria (36). iDFS is a composite endpoint that has been frequently used in published adjuvant eBC trials to date (36-40). In addition, iDFS events were not only based on clinical/radiological assessment, but also on confirmed histological/cytological assessment (unless there was an unacceptable risk to the patient due to the procedure).

Although the goal of adjuvant treatment is ultimately to improve OS, iDFS/DFS is an important endpoint, because reduction in recurrences will reduce mortality risk and morbidity related to recurrences. After introduction of the STEEP criteria, iDFS was adopted as an objective, well-accepted primary endpoint in eBC trials (41). Overall survival is considered the gold stand for oncology trials but represents several challenges in the field of adjuvant treatment in eBC. The primary challenge is the long follow-up time required to observe enough events, which has become even more difficult, as multiple therapies are approved both in eBC and aBC. This challenge is reflected in a recent Danish RWE analysis, where patients diagnosed with aBC have a median OS of more than 4.5 years when receiving ribociclib (42). The recent survival improvements in aBC are driven largely by CDK4/6 therapy, which was similarly introduced because of large improvement in PFS without any initial data substantiating OS improvement, closely resembling the current situation in eBC. Due to improved treatment practices, it is estimated that it can take a decade before improvements in OS can reliably be confirmed in eBC. It would not be practical or ethical to wait for OS to serve as the primary endpoint of adjuvant trials in eBC, especially taking into consideration the robustness of iDFS as a surrogate for OS.

Untch *et al.* has conducted a correlation analysis to evaluate iDFS/DFS as surrogate for OS in the adjuvant treatment of HR+/HER2−eBC (35). This was a two-part analysis: a trial-level relationship between treatment effects on iDFS/DFS and OS based on randomized controlled trials (RCTs) identified via an SLR, and a confirmatory outcome-level analysis based on patient level data from the randomized phase III FACE study (NCT00248170) (43). Trial-level analysis included 14 RCTs encompassing 31,668 patients, and demonstrated a significant, positive correlation between OS and DFS (Spearman coefficient unweighted 0.81 (95% CI. 0.56–0.94), and weighted 0.81 ($P<0.001$); R^2 weighted least squares = 84%) (35). Results of the scenario analysis (n = 9 RCTs), which excluded all chemotherapy (CT) trials, were consistent with the base case analysis. In addition, outcome-level analysis among patients of FACE trial (n = 3365) demonstrated positive correlation between OS and DFS event times as assessed by rho coefficient from the iterative multiple imputation (IMI) method (0.89; 95%CI: 0.87–0.92). Overall, these results reinforce using DFS or iDFS as a statistically valid surrogate endpoint for OS in the adjuvant HR+/HER2−eBC setting.

Table 9 Correlation between DFS and OS: Trial level analysis

Analysis	Unweighted correlation (95% CI)	Weighted Pearson[a] (SE)	Weighted Spearman[a]	R2 (OLS)	R2 (WLS)	STE
Base case	S: 0.81 (0.56-0.94) Pe: 0.71 (0.37-0.86)	0.78 (0.16) P<0.001	0.81 P<0.001	0.63 P<0.001	0.84 P<0.001	0.82
RCTs with CT trials excluded	S: 0.76 (0.26-0.98) Pe: 0.84 (0.54-0.95)	0.86 (0.15) P<0.001	0.82 P<0.001	0.76 P<0.001	0.86 P<0.001	0.78

Abbreviations: OLS, ordinary least squares; Pe, Pearson correlation; S, Spearman correlation; SE, standard error; STE, standard threshold effect; WLS, weighted least squares. a For weighted correlation, SE of OS is used as weight.

In addition, a study by Graff *et al.* (2024) evaluated iDFS as a surrogate for OS in the HR+/HER2−eBC adjuvant treatment setting at the outcome level in a real-world setting. Analysis was based on 3,133 US patients with HR+/HER2−eBC who had undergone surgery and initiated adjuvant ET identified in a Concert' AI database (academic and community setting). A significant and high correlation was observed between iDFS and OS in the overall cohort (IMI rho 0.83, P<0.001; Pearson 0.91, P<0.001; Spearman 0.88, P<0.001), with 82% of variation in OS explained by iDFS (least square R^2=0.82; (34). The results were consistent among all reported subgroups (key subgroups, e.g. NSAI monotherapy, TAM monotherapy, Neo(adjuvant) CT (yes/no), radiation therapy (yes/no). Thus, this retrospective cohort analysis supports a very strong patient-level surrogacy between iDFS and OS and the use of iDFS as an endpoint in HR+/HER2− eBC trials (34). Overall, we view the totality of evidence for iDFS as a surrogate to be strong and robust, therefore warranting the use as a primary endpoint and for modelling OS-benefit in the health economic analysis. In addition, as noted by the consulted clinical expert, most events accounted for by iDFS are distant recurrences both in NATALEE population (Table 24), but also in the DBCG cohort both for patients ≥ 70 years and < 70 years (Figure 51). Distant recurrences are considered unambiguously as incurable disease, and consequently based on logical deduction a strong correlation should exist between iDFS, DDFS or DRFS and OS.

4. Health economic analysis

4.1 Decision problem

The health economic analysis addresses the value of treating HR+/HER2-eBC patients in the adjuvant setting with RIB + ET compared with ET only.

4.2 Model applicability

This section describes the economic model evaluating the cost-effectiveness of RIB + ET as adjuvant treatment for HR+/HER2-eBC based on results of the NATALEE trial with data cut-off (DCO) April 29, 2024 (9).

The population evaluated in the model is adult (i.e., aged at least 18 years) men and women of known menopausal status receiving adjuvant treatment for HR+/HER2-eBC with Anatomic Stage II (IIA with either N0 with or without grade 2-3 tumors, or N1; IIB) or Stage III following successful surgical resection, consistent with the eligibility criteria of the NATALEE trial (44).

The model assumes that men and premenopausal women receiving an AI also receive gonadal suppression by GnRH agonists (e.g. goserelin). With the addition of a GnRH, these patients will have estrogen levels like those for postmenopausal women. As such, menopausal status is unlikely to be a treatment effect modifier. Additionally, there was no statistically significant difference in treatment effects detected for iDFS between pre- and postmenopausal patients in the NATALEE trial (5).

The economic model was developed in Microsoft Excel® to evaluate the cost-effectiveness of RIB + ET versus ET as adjuvant treatment for HR+/HER2-eBC. The model considers direct healthcare costs attributed to the treatment of eBC. The model is purposed for global use and has been adapted to conform with the methods and requirements of DMC.

The population evaluated in the model corresponds to the planned indication for ribociclib in combination with ET, which is intended to be used as adjuvant treatment for patients with HR+/HER2-eBC, consistent with the inclusion criteria and intervention examined in the phase 3 NATALEE trial (45).

4.3 Model Structure

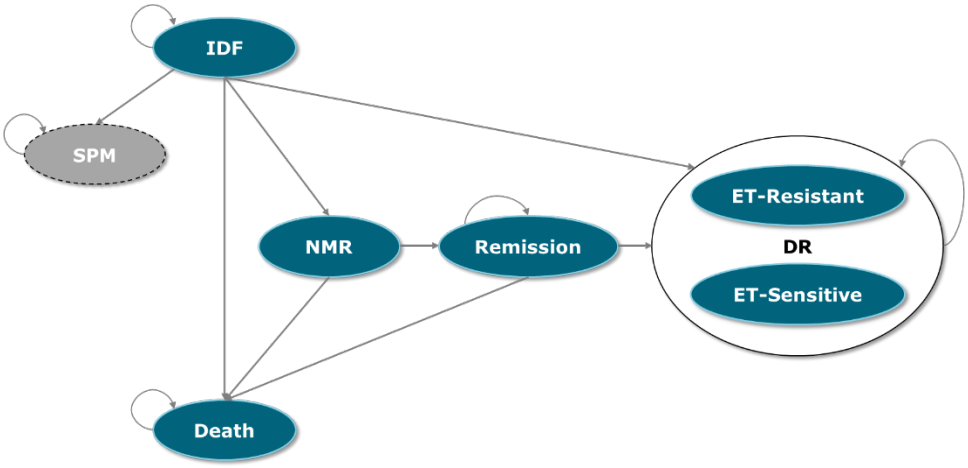
The model structure used in this evaluation is based on that of a previous model of abemaciclib as adjuvant treatment for high-risk HR+/HER2-eBC (46). A non-homogeneous, semi-Markov cohort model was employed, with states defined on disease recurrence and death. Non-homogeneous models include time-dependent transition matrices, which are required when age-specific mortality rates are used. Semi-Markov models allow the inclusion of tunnel states with transition probabilities defined on time since entering a state, which may be required for states wherein the probability of transition out of the state increases or decreases over time since entry into the state.

The model includes 6 health states defined based on disease-free status, type of recurrence (i.e., non-metastatic or distant), and vital status (alive or dead):

- Invasive disease-free (IDF); Second Primary Malignancy (SPM); Non-metastatic recurrence (NMR); Remission; Distant recurrence (DR); and Death

A simplified schematic depicting the model structure is shown in Figure 1.

Figure 1 Simplified Schematic of Markov Model Structure



IDF: Invasive disease-free; NMR: Non-metastatic recurrence; SPM: Second primary malignancy; DR: Distant recurrence; ET: Endocrine Therapy.

Patients are assumed to enter the model in the IDF state. In each model cycle, patients in the IDFS state either remain in that state, experience non-metastatic recurrence (i.e., locoregional recurrence, contralateral recurrence, or SPM), experience distant recurrence, or die. The NMR and Remission states include enough tunnel states to permit the probabilities of further progression and death to vary by duration of state membership (one year of tunnels, each). Locoregional and contralateral recurrence results in transit to the NMR state and distant recurrence results in transit to the DR state. Patients who die transition to the death state. The model does not include explicit health states for on- and off-treatment while in IDFS but has the facility to partition patients remaining in this state into on- and off-treatment based on the TTD curve. The model also considers stopping rules, where patients remaining in IDFS after a pre-specified duration are assumed to no longer be receiving treatment.

Patients who develop a SPM are assumed to enter an absorbing state, incurring a one-off cost of diagnosis, and then leave the model. Patients in the NMR state in each cycle either remain in that state or die. Patients who remain in the NMR state for a year will transition to the remission state. Those who enter the remission state may either remain in that state, experience distant recurrence or die. Patients who experience distant recurrence will transit to the DR state. Patients who die transition to the dead state.

Patients experiencing DR may enter one of two substates, which are modeled as absorbing states and stratified by the timing of recurrence: Those with recurrence ≤ 12 months from the end of ET were assumed to enter the ET-resistant substate, while those with recurrence > 12 months after the end of ET were assumed to enter the ET-sensitive substate. In the model base case, the logic applied for the cut-off defining ET-sensitive metastatic disease was first recurrence at least 72 months after starting adjuvant treatment, given that adjuvant ET was expected to be received for 60 months. To the extent that patients may discontinue ET earlier than 60 months (e.g., due to toxicity), the same rule of 72 months was applied. Furthermore, it was assumed that a patient who was coded as ET-resistant at first recurrence (i.e., non-metastatic recurrence occurring at < 72 months) could not later be considered as ET-sensitive.

Those entering either of the DR states received a fixed pay-off for LYs, time on treatment, QALYs, and costs. LYs and time on treatment in DR were modeled via a partitioned survival framework using PFS, TTD, and OS data from MONALEESA-2 (i.e., for ET-sensitive) and MONALEESA-3 (i.e., for ET-resistant). Extrapolations of PFS were used to calculate the proportions of patients in PFS by time since DR. Proportions of patients in PPS were calculated as the difference between extrapolated OS and PFS curves. LYs were then calculated based on expected PFS and PPS and time on treatment was calculated based on extrapolated TTD. QALYs in DR were calculated by multiplying expected pre- and post-progression LYs by health state utilities for PFS and PPS, respectively. Costs of subsequent treatments in DR were calculated from expected time on treatment and other costs related to healthcare resource use for metastatic breast cancer were calculated based on estimated frequency of healthcare services and unit costs.

4.3.1 Modelling of IDFS outcomes

For patients receiving RIB + ET and ET only, iDFS transition probabilities (transition to SPM, NMR, DR, and death) were estimated based on parametric survival distributions fit to patient-level failure time data using patient-level data on IDFS from the NATALEE trial (DCO April 29, 2024). Details on the curve fitting methods and results are presented in section 8, with a detailed overview in Appendix D.

In each model cycle, probabilities of transitioning from IDFS to the SPM, NMR, DR, and Death health states were calculated by multiplying the IDFS hazard rate by the distribution of IDFS events by type (i.e., with types of events corresponding to the model health states).

The distribution of IDFS events was assumed to be constant over time; however, probabilities of transitioning to the Death state were adjusted for general population mortality, with sex- and age-specific lifetables applied as a floor. As such, the proportion of transitions out of IDFS that transit to Death increases over time (i.e., relative to the proportion of transitions into other health states), as the model population ages. The distribution of IDFS events by type for RIB + ET and ET only are available from two sources: NATALEE and from the DBCG data presented in Appendix K. In NATALEE, data is available for both arms, whereas the DBCG data covers all patients treated in Denmark for eBC. Consequently, these patients could also have received other interventions than a NSAI and have not been treated with a CDK4/6 inhibitor. Using NATALEE data ensures the integrity of the data used to inform the IDFS curve, since these are tied to the events observed in

NATALEE and of which the IDFS extrapolation has been made. Conversely, the Danish data reflects what has been observed in the real-life treatment setting, which is impacted by the guidelines and treatment practices specific to Denmark.

Table 10 Distribution of IDFS Events by health state in NATALEE and in the DBCG cohort

	Number of Events	NMR	DR	SPM	Death
NATALEE					
RIB + ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DBCG data					
Danish patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ITT: intention to treat; ET: endocrine therapy; NMR: non-metastatic relapse; DR: Distant relapse; SPM: secondary primary malignancy; DBCG: Danish breast cancer group

Patients in the IDFS state were partitioned into on and off treatment, using the TTD curve from the NATALEE trial.

4.3.2 Non-Metastatic Recurrence and Remission States

Transition probabilities from the NMR state to death were assumed to be the same as the probability of death for the general population using the probability of death estimated from the IDFS curve as a floor. Patients who remain alive in the NMR state for a year transition to the remission state. The probability of death in the remission state was similarly assumed to be equal to that of the general population using the IDFS probability of death as a floor.

The use of IDFS as a floor for these two health states was programmed as a modelling option and was selected in the base case as to not overestimate effectiveness. The probability of distant recurrence within the remission state was estimated consistently with that in TA810 NICE appraisal of abemaciclib (46). The primary source for this parameter was NICE TA632 of trastuzumab, which used a published study of 12,836 eBC patients and estimated the risk of the incidence of a second malignancy after receipt of adjuvant therapy (47). The monthly transition probability of 0.0076 was calculated from a mean time until progression of 7.6 years (48).

4.3.3 Secondary primary malignancy

The SPM health state was modelled as an absorbing state, with no cost or QALYs payoffs within the state.

4.3.4 Distant Recurrence States

The DR substates (ET-sensitive and ET-resistant) were modelled as absorbing states and patients who entered these states received a fixed payoff of PFS and PPS LYs, and time on treatment, depending on the type of treatment received, calculated by embedded partitioned survival models (PSMs). The PSMs include the following states: PFS, PPS, and death. The PSM for the ET-sensitive substate (DR ≥12 months after completing adjuvant

treatment) was informed by data from MONALEESA-2 trial (49). The PSM for the ET-resistant substate (DR < 12 months from completing adjuvant treatment) was informed by data from the MONALEESA-3 trial (50).

The parametric survival distributions used in the PSMs were previously estimated using patient-level failure time data for PFS, OS, and TTD from the MONALEESA-2 and MONALEESA-3 trials. PFS, OS, and TTD curves for DR in the present model were re-estimated using the latest data cutoffs of MONALEESA-2 and MONALEESA-3. A detailed description of extrapolation methods is presented in Appendix D.

Undiscounted LYs were calculated for PFS and PPS states, with adjustments for general population mortality. Medication acquisition costs were calculated by multiplying estimated costs per cycle by the corresponding TTD curves. Follow-up and monitoring costs were calculated by multiplying per cycle costs of healthcare resources use in DR by the OS curves. PPS treatment costs were calculated by multiplying the estimated per-cycle cost of such treatments by the PPS curves. Terminal care costs were accrued by patients who died, calculated in each cycle as the probability of OS in the prior cycle minus the probability of OS in the current cycle and multiplied by the estimated cost of terminal care. All costs in the PSM were calculated on an undiscounted basis.

Outputted LYs and costs generated by the PSMs were then used as fixed payoffs upon entry into the Markov DR states. First, the weighted average DR LYs for each comparator were calculated by taking the sum of the product of LYs generated by the PSMs and the treatment mix in DR corresponding to that comparator. DR QALYs were then calculated by multiplying the DR LYs by corresponding health state utilities for PFS and PPS, adjusted for the model age at the time of DR. Payoffs for the different types of costs in DR were calculated similar to the approach used for LYs, by taking the sum of the product of costs from the PSMs and the mix of DR treatments for the corresponding comparator. The PSM fixed payoffs for LYs, QALYs, and costs were discounted at the time of entry into the Markov DR state.

4.4 Model features

Table 11 Features of the economic model

Model features	Description	Justification
Model Type	Semi-Markov Cohort Model with PSM modules	Semi-Markov models allow the inclusion of tunnel states with transition probabilities defined on time since entering a state
Patient population	Patients receiving adjuvant treatment for HR+/HER2- eBC who after surgical resection, tumor was completely removed and belongs to one of the following: stage IIA with either N1 or; N0 grade 3 or grade 2; stage IIB; or stage III	Trial inclusion criteria
Perspective	Limited societal perspective	According to DMC guidelines

Model features	Description	Justification
Time horizon	All outcomes were evaluated over a lifetime time horizon of 40 years.	To capture all health benefits and costs in line with DMC guidelines.
Cycle length	28 days	Consistent with length of treatment cycle (day 1 every 14 days).
Half-cycle correction	Yes	Outcomes has been half-cycle corrected, whereas costs have not as per DMC guidelines.
Discount rate	3.5% for the first 35 years 2.5% after 35 years	According to DMC guidelines
Intervention	Ribociclib 400 mg plus ET (letrozole 2.5 mg or anastrozole 1 mg) and, for men and premenopausal women only, goserelin 3.6 mg	Trial comparator consistent with Danish clinical practice
Comparator(s)	Endocrine therapy: Anastrozole Letrozole Exemestane and TAM (scenario)	According to national treatment guideline. Validated by Danish clinical expert
Effectiveness outcomes	Total LYs. Total QALYs.	
Costs	Drug acquisition costs; Medication administration costs and dispensing fees; Subsequent treatments costs (i.e., after recurrence); Follow-up and monitoring costs; Adverse event (AE) costs; and Terminal care costs.	
Cost-effectiveness	Cost per QALY gained (i.e., incremental for RIB + ET versus ET only); The primary measure of cost-effectiveness was the incremental cost-effectiveness ratio (ICER)	
Discounting	Costs and QALYs were discounted at an annual discount rate of 3.5% for the first 35 years and 2.5% from year 35 onwards.	DMC guideline

5. Overview of literature

5.1 Literature used for the clinical assessment

The clinical assessment of efficacy, safety and HRQoL will rely on the NATALEE trial, a randomized, controlled, phase III trial conducted to directly compare the safety and efficacy of ribociclib in combination with ET versus ET alone in adjuvant treatment for high-risk HR+/HER2-eBC [2]. The NATALEE trial was a head-to-head trial. It therefore provides the most relevant and suitable evidence representative of the Danish clinical practice, and therefore no SLR was used to inform the clinical section of this submission, as in accordance with the DMC guidelines. While no peer-reviewed publication has been made of the 4-year landmark analysis, this is expected to occur prior to the recommendation decision by the DMC.

Table 12 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Data on file. Novartis Pharmaceuticals. A phase III, multicenter, randomized, open-label trial to evaluate efficacy and safety of ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor positive, HER2-negative, early breast cancer: End of Ribociclib Analysis Report (4-year landmark). 2024. (9)	NATALEE	NCT03701334	Start: 07-12-2018 Completion: 29/05/2026 Data cut-off 29/04/2024 Future data cut-offs: no prespecified but at least one additional analysis will be conducted	RIB + ET vs. ET. Efficacy and safety data for 4-year landmark data
Conference abstract/presentation. Peter A. Fasching. LBA13 Adjuvant ribociclib (RIB) plus nonsteroidal aromatase inhibitor (NSAI) in patients (Pts) with HR+/HER2− early breast cancer (EBC): 4-year outcomes from the NATALEE trial. Ann Oncol. 2024;35:S1207. (7)	NATALEE	NCT03701334	See above	RIB + ET vs. ET. Efficacy and safety data for 4-year landmark data
Fasching PA, Slamon D, Nowecki Z*, et al.* Health-related quality of life in patients with HR+/HER2− early breast cancer treated with ribociclib plus a nonsteroidal (10)	NATALEE	NCT03701334	Data cut-off 11/01/2023	RIB + ET vs. ET. PRO data in HRQoL

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Data on file. Unpublished data. Novartis Pharmaceuticals. A phase III, multicenter, randomized, open-label trial to evaluate efficacy and safety of ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, HER2-negative, early breast cancer: efficacy analysis and safety update (11-Jan-2023 data cut-off). 2023. (51)	NATALEE	NCT03701334	Data cut-off 11/01/2023	RIB + ET vs. ET. PRO data in HRQoL

Additional publications are available for NATALEE, but these are older data-cuts for safety and efficacy and are consequently not used in the dossier (5, 6).

5.2 Literature used for the assessment of health-related quality of life

The utility values used in the health economic model were mainly derived from the clinical data from NATALEE as described in section 9.1. For adverse events, the disutilities were taken from the TA810 health economic assessment from NICE.

Table 13 Relevant literature included for (documentation of) HRQoL (See section 9.1)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Fasching PA, Slamon D, Nowecki Z, et al. Health-related quality of life in patients with HR+/HER2− early breast cancer treated with ribociclib plus a nonsteroidal aromatase inhibitor: results from the NATALEE trial. Clinical Cancer Research. 2025. (10)	EQ-5D-5L data used to establish health states utility values for the eBC setting in the CUA.	NATALEE PRO data comparison in Section 10 for EQ-5D-5L and EORTC QLQ-C30 functional domain (physical functioning). EQ-5D-5L measurements also used to establish the health state utility values in the eBC setting in the CUA.
pan-Canadian Oncology Drug Review - *Final Economic Guidance Report - Ribociclib (Kisqali) for Metastatic Breast Cancer*. 2018 (49)	PPS DR ET sensitive Utility factor	Section 10.4
pan-Canadian Oncology Drug Review. Final Economic Guidance Report - Ribociclib (Kisqali) plus Fulvestrant for Advanced or Metastatic Breast Cancer. 2020 (52)	PPS DR Sensitive Utility factor	Section 10.4

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
National Institute of Health and Care Excellence. Abemaciclib with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence [TA810]. 2022 (46)	AE disutilities	Section 10.4

5.3 Literature used for inputs for the health economic model

Table 14 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Neven P, Fasching PA, Chia S, et al. Updated overall survival from the MONALEESA-3 trial in postmenopausal women with HR+/HER2- advanced breast cancer receiving first-line ribociclib plus fulvestrant. Breast cancer research : BCR. 2023;25(1):103. (50)	OS/PFS/TTD curves in the DR state	Targeted literature review	Appendix D
Cristofanilli M, Rugo HS, Im SA, et al. Overall Survival with Palbociclib and Fulvestrant in Women with HR+/HER2-ABC: Updated Exploratory Analyses of PALOMA-3, a Double-blind, Phase III Randomized Study. Clinical cancer research : an official journal of the American Association for Cancer Research. 2022;28(16):3433-42. Cristofanilli M, DeMichele A, Giorgetti C, et al. Predictors of prolonged benefit from palbociclib plus fulvestrant in women with endocrine-resistant hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer in PALOMA-3. Eur J Cancer. 2018;104:21-31. (53, 54)	HR for OS/PFS/TTD curves in the DR state	Systematic literature review	Appendix D and
Sledge GW, Jr, Toi M, Neven P*, et al.* The Effect of Abemaciclib Plus Fulvestrant on Overall Survival in Hormone Receptor–Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy—MONARCH 2: A Randomized Clinical Trial. JAMA Oncology. 2019. Sledge GW, Jr., Toi M, Neven P, et al. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. J Clin Oncol. 2017;35(25):2875-84 (55, 56)	HR for OS/PFS/TTD curves in the DR state	Systematic literature review	Appendix D

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Di Leo A, Jerusalem G, Petruzelka L, et al. Final overall survival: fulvestrant 500 mg vs 250 mg in the randomized CONFIRM trial. J Natl Cancer Inst. 2014;106(1):djt337-djt. (57)	HR for OS/PFS/TTD curves in the DR state	Systematic literature review	Appendix D
Johnston SR, Kilburn LS, Ellis P, et al. Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors in postmenopausal patients with hormone-receptor-positive locally advanced or metastatic breast cancer (SoFEA): a composite, multicentre, phase 3 randomised trial. Lancet Oncol. 2013;14(10):989-98. (58)	HR for OS/PFS/TTD curves in the DR state	Systematic literature review	Appendix D
Piccart M, Hortobagyi GN, Campone M, et al. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2. Ann Oncol. 2014;25(12):2357-62. (59)	HR for OS/PFS/TTD curves in the DR state	Systematic literature review	Appendix D
Hortobagyi G, Stroyakovskiy D, Yardley D. Ribociclib + nonsteroidal aromatase inhibitor as adjuvant treatment in patients with HR+/HER2− early breast cancer. 2023 San Antonio Breast Cancer Symposium; Presented December 8, 2023. (60)	HR OS/PFS/TTD curves in the DR state	Systematic literature review	Appendix D
Rugo HS, Turner NC, Finn RS, et al. Palbociclib plus endocrine therapy in older women with HR+/HER2- advanced breast cancer: a pooled analysis of randomised PALOMA clinical studies. Eur J Cancer. 2018;101:123-33. Slamon DJ, Dieras V, Rugo HS, et al. Overall Survival With Palbociclib Plus Letrozole in Advanced Breast Cancer. J Clin Oncol. 2024;42(9):994-1000. (61, 62)	HR for OS/PFS/TTD curves in the DR state	Systematic literature review	Appendix D
Goetz MP, Cicin I, Testa L, et al. Impact of dose reductions on adjuvant abemaciclib efficacy for patients with high-risk early breast cancer: analyses from the monarchE study. NPJ Breast Cancer. 2024;10(1):34. (63)	HR for OS/PFS/TTD curves in the DR state	Systematic literature review	Appendix D
Robertson JF. Final overall survival analysis for fulvestrant vs anastrozole in endocrine therapy (ET)-naive, hormone receptor-positive (HR+) advanced breast cancer (FALCON). Annals of Oncology. 2023. (64)	HR for OS/PFS/TTD curves in the DR state	Targeted literature review	Appendix D

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Mouridsen H, Gershanovich M, Sun Y, et al. Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. J Clin Oncol. 2003;21(11):2101-9.(65)	HR for OS/PFS/TTD curves in the DR state	Targeted literature review	Appendix D
Nabholtz J, Buzdar A, Pollak M, et al. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. J Clin Oncol. 2000;18(22):3758-67. (66)	HR for OS/PFS/TTD curves in the DR state	Targeted literature review	Appendix D
Bonneterre J, Thurlimann B, Robertson J, et al. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. J Clin Oncol. 2000;18(22):3748-57. (67)	HR for OS/PFS/TTD curves in the DR state	Targeted literature review	Appendix D
Lu YS, Mahidin E, Azim H, et al. Final Results of RIGHT Choice: Ribociclib Plus Endocrine Therapy Versus Combination Chemotherapy in Premenopausal Women With Clinically Aggressive Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer. J Clin Oncol. 2024;42(23):2812-21. (68)	HR for OS/PFS/TTD curves in the DR state	Targeted literature review	Appendix D
National Institute of Health and Care Excellence. Committee Papers [TA632]: Single Technology Appraisal Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer [ID1516]. (47)	Non-metastatic remission (NMR); recurrence rates	Targeted literature review	4.3.2
DBCG. Data on file: Final data report ER+/HER- eBC stage II-III. 2025.(3)	Type of event from IDFS state (scenario analysis), Age, Epidemiology data	Local data	Appendix K

6. Efficacy

This chapter is based entirely on the NATALEE trial. Results for the ITT population are provided, with additional subgroup analyses presented for the primary endpoint, iDFS. Subgroup analyses are presented to justify homogeneous efficacy and will not be presented in Appendix B, nor will any health economic analysis be conducted for subgroups, as the demonstrated efficacy is not statistically or clinically different from the ITT results.

6.1 Efficacy of ribociclib plus ET compared to ET only for patients with HR+/HER- EBC at high risk of recurrence

6.1.1 Relevant studies

6.1.1.1 NATALEE trial

Trial rationale

Treatment of patients with HR+/HER2−eBC is administered with curative intent, however disease recurrence remains a significant problem, especially within a broader population of patients with stage II and stage III disease (4), see section 3.1. The need for treatments that address recurrence in a broader population must also be balanced with a manageable safety profile for use in the adjuvant setting. Therefore, a significant unmet need remains for these patients.

Many breast cancer treatments approved for use in the adjuvant setting have initially demonstrated efficacy in aBC (69). In recent years, the introduction of CDK4/6i added to ET has improved outcomes for patients with HR+/HER2−aBC. CDK4/6i added to ET has become a standard of care for first-line treatment of HR+/HER2−aBC (70). For ribociclib, the evidence is based on the three large phase III MONALEESA trials. In all three trials, RIB + ET demonstrated significant PFS and OS benefit in patients with HR+/HER2−aBC (71-77). In addition, RIB + ET was associated with an acceptable safety profile compared with ET alone in all MONALEESA trials. Taken together, the efficacy and safety profile of ribociclib in the advanced setting suggested that ribociclib may address unmet needs among patients with HR+/HER2−eBC.

Other CDK4/6 inhibitors, palbociclib (PALLAS and PENELOPE-B trials) and abemaciclib (monarchE trial), have been tested in the HR+/HER2−eBC population, but only abemaciclib demonstrated significant iDFS benefit compared with ET alone (39, 78-82). The monarchE trial specifically targeted high-risk patients with node-positive early breast cancer -either N2/N3 or N1 with additional high-risk factors such as tumor size ≥ 5 cm, histologic grade 3, or Ki-67 ≥ 20%. It did leave out a significant proportion of N1 patients and did not include node-negative patients, thus excluding a significant group who also faces a substantial and less recognized high risk of recurrence as demonstrated by the DBCG registry data (see

section 3.1). By contrast, the NATALEE trial was designed to address this gap by including all high-risk node-negative patients, acknowledging their considerable unmet treatment needs alongside those of all node-positive patients. As abemaciclib is not used as a comparator in this assessment, the differences between patient populations in NATALEE and monarchE trial are only discussed in Appendix M. Direct comparison of efficacy estimates from NATALEE and monarchE are biased and not possible due to differences in the population and comparator selection, which is also discussed in Appendix M .

Rationale for choice of ribociclib dosing

The dosing regimen for ribociclib used in eBC differs from aBC where the approved dosing is 600 mg once daily for 21 days, followed by 7 days off. The 400 mg dose was chosen for eBC based on the exposure response models from the advanced (metastatic) (aBC) studies of ribociclib, in which the results indicated a potentially improved safety profile of the 400 mg starting dose in terms of dose-dependent toxicities such as QTc prolongation and myelosuppression compared with the 600 mg dose (71). Additionally, post hoc exploratory analyses were performed on the aBC trials of ribociclib in which patients whose dose was reduced from 600 mg to 400 mg continued to show a clinically meaningful treatment benefit compared with ET only (83).

Therefore, considering the totality of evidence from preclinical research and clinical evidence from the aBC, and given that the tumor burden in eBC is significantly lower than in aBC, it was hypothesized that the dose and duration implemented in the NATALEE study would optimize efficacy while improving tolerability.

Rationale for choice of ribociclib treatment duration

Recurrences in eBC are thought to be driven by a variety of mechanisms, including replicating circulating tumor cells and awakening of previously dormant micro metastatic disease (84, 85). In addition to inducing cell-cycle arrest, the unique senescence (irreversible cell-cycle arrest) and immunomodulatory properties of ribociclib may have the potential to prevent recurrences in patients with eBC through direct elimination of replicating tumor cells or by locking dormant tumor cells in a state of senescence and priming the immune system for eventual clearance of these cells. In ER+ disease, > 50% of recurrences occur beyond 5 years; therefore, tumor-cell dormancy may be long (86-88). Prolonging cell-cycle arrest may be critical to driving more tumor cells into senescence and eventual clearance by immune-mediated mechanisms. A 3-year duration of treatment was selected based on consistent efficacy in post hoc exploratory analyses from the MONALEESA program (MONALEESA-2, -3 and -7) (89). The 3-year treatment duration of ribociclib in the NATALEE trial is intended to maximize on-target exposure of circulating tumor cells or dormant micro metastatic disease to ribociclib, thereby preventing recurrences even after stopping ribociclib treatment.

Design and methodology

NATALEE is a global, Phase III, multicenter, randomized, open-label trial in adult women, regardless of menopausal status, and men with HR+/HER2−eBC. The NATALEE trial is evaluating the efficacy and safety of ribociclib plus standard adjuvant ET versus standard adjuvant ET alone. Men and premenopausal women also received goserelin. In total, 5,101 patients were randomized in a 1:1 ratio. Randomization was stratified by menopausal

status, anatomic stage II or III, prior (neo)adjuvant CT, and geographic region. The enrolment of patients with stage II disease was capped at 40%. Inclusion and exclusion criteria are reported in Appendix A. A diagram showing inclusion based on TNM-staging is presented in Appendix M, Figure 58.

Investigational arm consisted of: ribociclib (400 mg once daily on days 1–21 of a 28-day cycle plus ET). The ET can be:

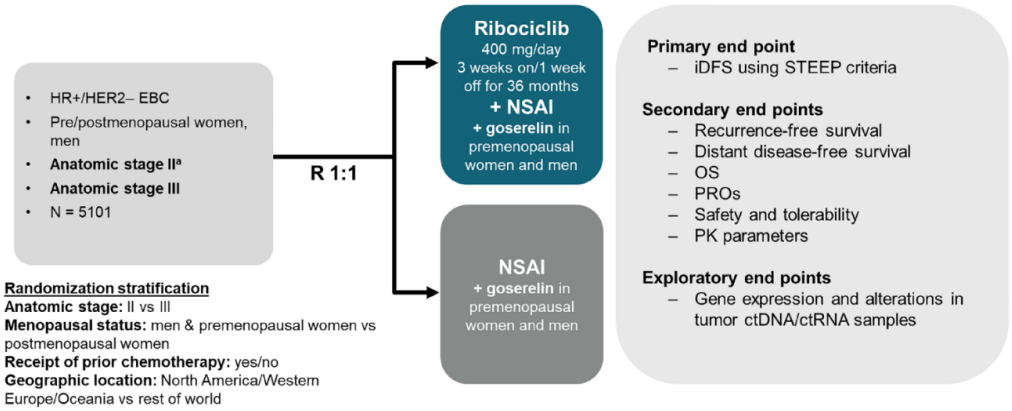
- Postmenopausal women: Letrozole (2.5 mg once daily) or anastrozole (1 mg once daily) on a continuous schedule for 60 months
- Premenopausal women and men: Letrozole (2.5 mg once daily) or anastrozole (1 mg once daily) plus goserelin (3.6 mg subcutaneously once every 4 weeks) on a continuous schedule for 60 months

Additional treatment with the et beyond 60 months was at the discretion of the treating physician and was not considered to be part of the trial treatment.

Control arm consisted of: ET as given above for the investigational arm.

The study consists of a 28-day screening phase, a 60-month treatment phase (including a 30-day safety follow-up), and a follow-up phase (including efficacy and survival assessments).

Figure 2 Overall study design of NATALEE



[a]Stage IIB or IIA that is either: N1 or N0 with: Grade 3 or Grade 2 with any of the following criteria: Ki67 ⩾ 20%, or Oncotype DX Breast Recurrence Score ⩾26, or categorized as high risk via Prosigna/PAM50, MammaPrint or EndoPredict EPclin Risk Score. ctDNA, circulating tumor DNA; ctRNA, circulating tumor RNA; NSAI, nonsteroidal aromatase inhibitor; PK, pharmacokinetic; PRO, patient-reported outcome; R, randomization

Study endpoints

The primary endpoint of the NATALEE trial is iDFS according to the STEEP criteria as assessed by the investigator. Secondary endpoints include RFS, DDFS, OS, frequency and severity of AEs, quality of life (QoL) as assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30), and pharmacokinetic parameters. The efficacy study endpoints and their definitions, validity and methodology are discussed in section 3.7.1 above.

Analysis sets

The Full analysis set (FAS), which are referred to as the ITT, is comprised of all patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients were analyzed according to the treatment and strata they had been assigned to during the randomization procedure. ITT analysis included 2,549 patients receiving RIB + ET and 2,552 patients receiving ET only. Unless otherwise noted, all efficacy results are ITT.

The Safety analysis set (SAS) included all randomized patients who received any study treatment (i.e., at least one dose of ribociclib or ET). Patients were analyzed according to the study treatment received. Safety analysis set included 2,525 patients receiving RIB + ET and 2,442 patients receiving ET only. Unless otherwise noted, all safety results are from the SAS.

Patient disposition

In total, 6,068 patients were screened, and 5,101 patients were enrolled from 20 countries and 393 sites. The median duration of exposure to the study treatment was comparable between the two treatment arms—45.1 months in the RIB + ET arm and 45.0 months in the ET only arm

At 4-year data cut-off (DCO: April 29, 2024), the median duration of exposure to ribociclib was 27.4 months (range: 0–37 months). As of this primary endpoint analysis cut-off date, 1,601 patients corresponding to 62.4% had completed the full 3-year treatment and all patients were off ribociclib. Overall, the patient disposition based on completion and discontinuation rates was balanced between the two treatment arms.

Table 15 Patient disposition, median follow-up of 44.2, with all patients of ribociclib

Subject	RIB + ET, N = 2,549, n (%)		ET alone, N = 2,552 n (%)
Randomized	2549 (100)		2552 (100)
Treated	2526 (99.1)		2441 (95.7)
NSAI treatment ongoing	1794 (70.4)		1628 (63.8)
Completed 3y RIB	1601 (62.8)		-
Competed 5y study treatment	10 (0.4)		9 (0.4)
Treatment discontinued	RIB	NSAI	NSAI
Early discontinuation	923 (36.2)	722 (28.3)	804 (31.5)
Primary reason for discontinuation			
AE	509 (20.0)	136 (5.3)	125 (4.9)
Distant relapse	127 (5.0)	196 (7.7)	267 (10.5)
Patient/Physician decision	160 (6.3)	206 (8.1)	189 (7.4)
Lost to follow-up	8 (0.3)	15 (0.6)	21 (0.8)
Death	5 (0.2)	9 (0.4)	6 (0.2)
*Other	114 (4.5)	160 (6.2)	197 (7.7)

*Other includes withdrawal by patient, protocol deviation, among other reasons

Table 16 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
NATALEE, NCT03701334 (5-10)	Randomized phase III	April DCO: median follow-up for iDFS (primary endpoint): 44.2 months, landmark analysis at 4 years.	Eligible patients were men or premenopausal or postmenopausal women who were ≥ 18 years and had histologically confirmed HR+/HER2- EBC according to local assessment. Patients were required to have stage II or III disease. The anatomical stage was derived with the use of tumor–node–metastasis (TNM) staging (for detailed information on TNM-staging and other selection criteria see section Appendix K)	Ribociclib (at a dose of 400 mg per day for 3 weeks, followed by 1 week off, for 3 years) plus a NSAI (see comparator)	ET; letrozole at a dose of 2.5 mg per day or anastrozole at a dose of 1 mg per day for ≥5 years) Premenopausal women and men had goserelin added	**Primary (4-year landmark analysis):** • iDFS using STEEP criteria, as assessed by Investigator **Secondary (4-year landmark analysis):** • RFS using STEEP criteria • DDFS using STEEP criteria • OS defined as time from date of randomization to date of death due to any cause • Change from baseline in the physical functioning sub-scale score and global health status/ QoL scale score as assessed by EORTC QLQ-C30 • Frequency and severity of AEs, laboratory and ECG **Exploratory:** • LRRFS • DRFS • Incidence of subsequent antineoplastic therapy and time to first subsequent antineoplastic therapy • Number of patients hospitalized, total number of hospitalizations, and length of stay in hospitals, number of patients with Emergency Room and additional visits

6.1.2 Comparability of studies

Not relevant for comparisons only based on head-to-head studies.

6.1.2.1 Comparability of patients across studies

Baseline characteristics were well balanced between the two treatment arms. Patients were representative of the population of pre- and postmenopausal women and men with HR+/HER2−eBC. The median age of the patients was 52 years, with 34.2% of patients within the 45–54 years age group. Overall, 99.6% of patients were women and 0.4% were men. Extended demographic characteristics, disease characteristics and prior treatment patterns are given in Appendix L.

Table 17 Selected baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	Baseline characteristics	RIB + ET N=2,549, n (%)	ET only N=2,552, n (%)	Total N=5,101, n (%)
Age	Age, mean (SD)	52.9 (10.75)	52.7 (10.77)	52.8 (10.76)
	Age, median (min–max)	52.0 (24–90)	52.0 (24–89)	52.0 (24–90)
Gender	Female	2,538 (99.6)	2,543 (99.6)	5,081 (99.6)
Menopausal status	Premenopausal women and men	1,125 (44.1)	1,128 (44.2)	2,253 (44.2)
	Postmenopausal women	1,424 (55.9)	1,424 (55.8)	2,848 (55.8)
ECOG	PS 0	2,106 (82.6)	2,132 (83.5)	4,238 (83.1)
	PS 1	440 (17.3)	418 (16.4)	858 (16.8)
Grade at diagnosis	GX	30 (1.2)	32 (1.3)	62 (1.2)
	G1	218 (8.6)	240 (9.4)	458 (9.0)
	G2	1,458 (57.2)	1,451 (56.9)	2,909 (57.0)
	G3	521 (20.4)	549 (21.5)	1,070 (21.0)
T-stage at diagnosis	TX	175 (6.9)	173 (6.8)	348 (6.8)
	T0	4 (0.2)	7 (0.3)	11 (0.2)
	Tis	2 (0.1)	3 (0.1)	5 (0.1)
	T1	471 (18.5)	442 (17.3)	913 (17.9)
	T2	1,181 (46.3)	1,235 (48.4)	2,416 (47.4)
	T3	471 (18.5)	472 (18.5)	943 (18.5)
	T4	200 (7.8)	184 (7.2)	384 (7.5)

	Baseline characteristics	RIB + ET N=2,549, n (%)	ET only N=2,552, n (%)	Total N=5,101, n (%)
N-stage at diagnosis	NX	272 (10.7)	264 (10.3)	536 (10.5)
	N0	694 (27.2)	737 (28.9)	1,431 (28.1)
	N1	1,050 (41.2)	1,049 (41.1)	2,099 (41.1)
	N2	332 (13.0)	292 (11.4)	624 (12.2)
	N3	151 (5.9)	175 (6.9)	326 (6.4)
Month since diagnosis	Mean (SD)	11.8 (3.53)	11.8 (3.58)	11.8 (3.55)
Prior CT	CT	2,249 (88.2)	2,245 (88.0)	4,494 (88.1)
Prior ET	ET	1,824 (71.6)	1,801 (70.6)	3,625 (71.1)
	AI	1,601 (62.8)	1,592 (62.4)	3,193 (62.6)
	Anti-estrogens	344 (13.5)	341 (13.4)	685 (13.4)
	Gonadotropin-releasing hormone analogs	670 (26.3)	620 (24.3)	1,290 (25.3)
Therapy setting	Adjuvant	2,160 (84.7)	2,150 (84.2)	4,310 (84.5)
	Adjuvant chemotherapy	1,223 (48.0)	1,220 (47.8)	2,443 (47.9)
	Neo-adjuvant	1,129 (44.3)	1,148 (45.0)	2,277 (44.6)
	Neo-adjuvant chemotherapy	1,085 (42.6)	1,095 (42.9)	2,180 (42.7)
	Number of patients who received any prior anti-neoplastic radiotherapy	2,292 (89.9)	2,302 (90.2)	4,594 (90.1)

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

Certain differences are observed between the DBCG cohort when compared to the NATALEE trial population (Table 18). These differences are largely driven by two factors, 1) local treatment practices in Denmark and 2) lower probability of elderly population to participate in a clinical trial.

The patients participating in NATALEE were younger, 52 years vs. 62 years in the DBCG registry. This age disparity is identical to the differences noted between the monarchE study population and the Danish patients in the DMC's assessment of abemaciclib (28). As suggested, this could lead to a slightly higher discontinuation rate in Danish patients as elderly patients tend to have lower tolerability to adverse events. However given the AE profile of ribociclib, which is mainly focused on laboratory abnormalities related to bone marrow suppression, the impact is deemed less important.

Patients in NATALEE and DBCG Cohort had similar N0 involvement but less overall lymph node involvement with N1 patients accounting for 42% in NATALEE vs. 67% in the DBCG Cohort, resulting in fewer (20%) N2-3 in the DBCG Cohort vs. 42% in NATALEE. Higher node-involvement in NATALEE would be expected, since the stage II patient population in NATALEE was restricted during enrollment by capping at 40% (≥ 60% stage III). Furthermore, the Danish treatment practice for axillary nodal status determination (SENOMAC) will also result in more N1 patients as fewer patients undergo complete surgical axillary examination.

Further Ki67-status was evaluated for approximately 37% of patients in NATALEE, however it was not used to decide if patients would be eligible (only for a very small subset of T2N0 patients with grade 2 tumors could Ki-67 status be considered an eligibility criterion for enrollment). Therefore, it does not skew the overall data or transferability, but was simply measured in the trial, whereas this is not done in the Danish population. Ki67 subgroup analysis did not confirm any differential effect based on Ki-67 ≤ 20% or Ki-67 > 20 % (8). The fact, that subgroup analysis did not reveal any subgroup effects based on Ki-67-status, and that Ki-67 was not generally used to determine who should enter the trial, confirms that there is no effect of Ki-67 measurements in NATALEE and the transferability of this data to the Danish population.

Table 18 Characteristics in the relevant Danish population and in the health economic model

Characteristics	Value in Danish population	Value used in health economic model
Age	62 (DBCG data)	60 (KOL opinion)
Gender	NA	99.60% female (NATALEE)
N0	14%	15%
N1	67%	42%
N2-3	20%	44%
Premenopausal	27%	44%
Postmenopausal	73%	56%
Chemotherapy (neo/adjuvant)	56%	88%
Tamoxifen*	31%	0%
Age, (median)	62	52

Overall, the observed differences in patient demographics and treatment patterns between real-world setting and the clinical trial cohort are unlikely to cause any difference in the observed effectiveness of ribociclib as adjuvant therapy. The consistent efficacy observed across diverse subgroups in the NATALEE trial supports the generalizability of ribociclib's benefit in combination with ET for HR+/HER2-negative high-risk, eBC patients regardless of variability in the baseline characteristics as noted in the subgroup analysis (see Table 25 and Appendix 0)

Looking at the outcomes of patients in the ET-only arm of NATALEE and the corresponding DBCG cohort treated with ET-only, confirms this notion of high transferability of the results, as iDFS, DDFS and OS rates at 3-years are very similar. In conclusion, although variability is noted in several baseline characteristics these are ultimately unlike to have

any meaningful impact when extrapolating the results from NATALEE to the Danish clinical context.

Table 19 3-year iDFS, DDFS and OS rates from NATALEE and DBCG cohort

Cohort	iDFS, 3-year rate (95% CI)	DDFS, 3-year rate (95% CI)	OS, 3-year rate (95% CI)
ITT NATALEE	88.1 (86.7–89.4)	91.6 (90.4-92.7)	96.0 (95.1-96.8)
DBCG cohort	[redacted]	[redacted]	[redacted]

6.1.4 Efficacy – results from NATALEE

An overview of efficacy analysis for the primary (iDFS), secondary (DDFS and OS) and the exploratory endpoint (DRFS) is provided in Table 20 all favoring the RIB + ET over ET only in the ITT population.

Table 20 Results from the comparative analysis of RIB + ET vs. ET only for ITT population

Efficacy outcomes*	RIB + ET, n = 2,549	ET only, n = 2,552	Results, ARR, HR (95%CI)
iDFS, 4-year	88.5% (87.1–89.8)	83.6% (81.8–85.2)	4.9%, 0.715 (0.609–0.840)
DDFS, 4-year	89.4% (88.0–90.7)	84.9% (83.2–86.5)	4.5%, 0.715 (0.604–0.847)
DRFS, 4-year	[redacted]	[redacted]	[redacted]
OS, 4-year	95.0% (94.0–95.9)	94.2% (93.0–95.2)	0.8%, 0.827 (0.636–1.074)

*median was not reached for any of the endpoints, 4-year rates provided. ARR = absolute risk reduction

Three data cuts have been analyzed and reported from NATALEE. At the protocol-specified second interim efficacy analysis, based on the P value of 0.0014, the independent data monitoring committee recommended to stop the formal statistical analysis of the primary endpoint, because the early stopping boundary for statistical significance was crossed (5). This analysis was therefore considered the principal analysis demonstrating the superiority of RIB + ET over ET only for iDFS. Additionally, a final protocol-specified analysis of iDFS occurred after 500 iDFS events and was first reported at SABCS 2023 (6). Finally, the most recent data cut was the exploratory 4-year landmark analysis which occurred after all patients had stopped ribociclib and was first reported at the European Society for Medical Oncology Congress [ESMO] in September 2024 (8, 9). Follow-up will continue, and efficacy and safety data will be collected for patients remaining in the study.

Table 21 NATALEE iDFS analyses over time

NATALEE Data Cuts	Type of analysis	Data cutoff	iDFS follow-up time, median, months	iDFS events
Second interim efficacy analysis (5)	Prespecified	Jan 11, 2023	27.7	426
Final iDFS analysis (6)	Prespecified	Jul 21, 2023	33.3	509
4-Year landmark analysis (8, 9)	Exploratory	Apr 29, 2024	44.2	603

The results from the 4-year landmark analysis, based on 603 iDFS events (data cut-off: April 29, 2024) are presented in this section (8, 9). The final iDFS analysis (509 events) included in the overview below in Table 22, only to contrast the treatment improvements seen as follow-up extends, and to document the increasing absolute treatment benefit seen beyond completion of 3-year ribociclib treatment. Further this increase substantiates the claim of the continued benefit of ribociclib as treatment benefit continues to increase over time after treatment cessation of ribociclib.

Primary endpoint — iDFS, final iDFS analysis vs. 4-y landmark analysis

Table 22 Final iDFS analysis, 4-year landmark analysis

Analysis, FU time	3-years, iDFS (%)		ARR	4-years iDFS (%)		ARR	95%, CI	P-value
	RIB+ET	ET		RIB+ET	ET			
Final iDFS, 33.3 mo.	90.8	87.6	Δ3.1 %	NA	NA	NA	0.749 (0.628-0.892)	.0006[a]
4-year landmark, 44.2 mo.	90.8	88.1	Δ2.7%	88.5	83.6	Δ4.9%	0.715 (0.609-0.840)	<.0001[a]

[a] P values are nominal since no adjustments were made for multiple comparisons after the second interim efficacy analysis. ARR = Absolut risk reduction

As of the 4-year landmark analysis data cut-off date (April 29, 2024), the median duration of follow-up for iDFS was 44.2 months. At the 4-year landmark analysis (performed at 603 iDFS events), the iDFS results met the criteria to demonstrate statistically significant and clinically superior efficacy of RIB + ET vs ET only.

A total of 263 patients (10.3%) in the RIB + ET arm had an iDFS event compared with 340 patients (13.3%) in the ET only arm. An estimated 28.5% relative reduction was observed in the risk of an iDFS event for patients in the RIB + ET arm compared with those in the ET only arm (hazard ratio: 0.715, 95% CI: 0.609−0.840).

The 4-year iDFS rates were 88.5% (95% CI: 87.1−89.8) in the RIB + ET arm and 83.6% (95% CI: 81.8−85.2) in the ET only arm, reflecting a 4.9% absolute benefit favoring RIB + ET (Table 23). Fewer distant recurrence events were reported in the RIB + ET arm compared with the ET only arm (6.9% vs 9.6%). A summary of iDFS in the ITT population at the time of the 4-year landmark analysis is shown in Table 23 (8, 9).

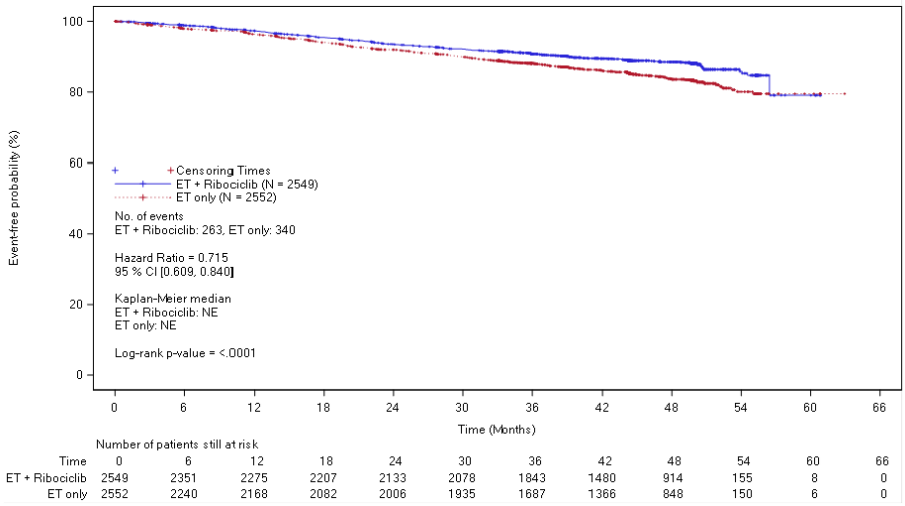
Table 23 Detailed Summary of iDFS in the ITT-population (4-year landmark analysis) (8, 9)

	RIB + ET, N=2,549	ET only, N=2,552
Median follow-up (months)	44.2	
Number of events, n (%)	263 (10.3)	340 (13.3)
Hazard ratio (95% CI), p-value	0.715 (0.609–0.840), <0.0001	
iDFS rate 12 months (95% CI)	97.3 (96.5-97.9)	96.3 (95.4-97.0)
iDFS rate 24 months (95% CI)	93.5 (92.4-94.4)	92.0 (90.8-93.0)

iDFS rate 36 months (95% CI)	90.8 (89.5–91.9)	88.1 (86.7–89.4)
iDFS rate 48 months (95% CI)	88.5 (87.1–89.8)	83.6 (81.8–85.2)

Figure 3 presents the KM iDFS curves for the 4-year landmark analysis. The curves start to diverge early and in general, the iDFS event-free probability remained higher in the RIB + ET arm, which indicated an early sustained benefit with RIB + ET. Breakdown of the KM-curve after 54 months is due to lack of follow-up and censoring (low number at risk), which is also the case for the other secondary endpoints.

Figure 3 Kaplan-Meier plot for iDFS (4-year landmark analysis)



Abbreviations: CI: Confidence Interval; ET: Endocrine Therapy; iDFS: Invasive Disease-Free Survival; NE: Not Estimable. Note: P-value from the stratified log-rank test is one-sided. Source: Novartis Data on File (4-year landmark Analysis) (8, 9).

Breakdown of iDFS endpoint – individual components

Not all events included in the iDFS endpoint are considered of equal severity and therefore a breakdown of the individual type of first iDFS events, as well as the percentage of patients experiencing the event is provided below along with and the relative portion of the events belonging to a particular iDFS event type (Table 24). Most events recorded as first events are distant recurrences and occurred in 176 out of 2,549 patients (6.9%) in the RIB + ET arm and therefore accounting for approximately 64% of all first events in the RIB + ET arm. Correspondingly in the ET only arm distant recurrences occurred in 246 out of 2552 patients (9.6%), and therefore accounting for approximately 67.4% of all first events.

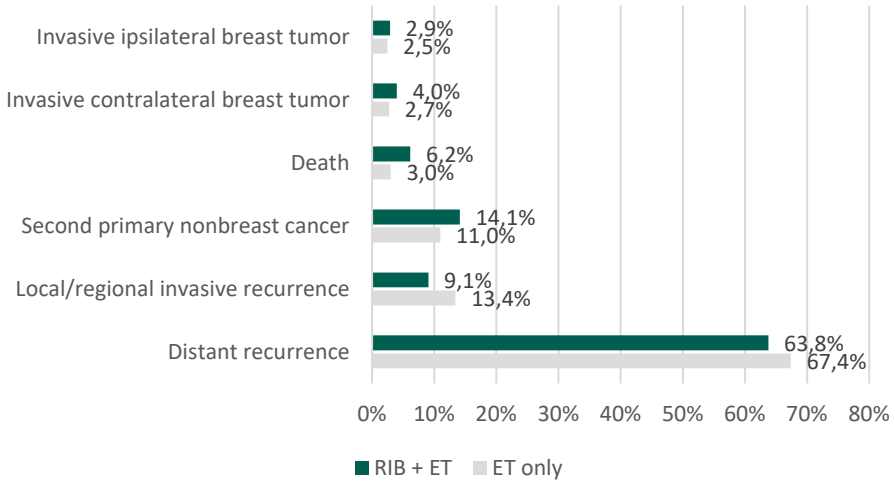
As seen in the breakdown most of the observed difference in the iDFS-rates is driven by fewer distant recurrences in the RIB + ET vs ET only arm (6.9% vs. 9.6%).

Table 24 Type of first iDFS events in the ITT population

Type and site of first iDFS event, reported; n (% patients; % of first event type)	RIB + ET, n = 2,549	ET Alone, n = 2,552
Distant recurrence	176 (6.9; 63.8)	246 (9.6; 63.8)
Local/regional invasive recurrence	25 (1.0; 9.1)	49 (1.9; 13.4)
Second primary non-breast cancer	39 (1.5; 14.1)	40 (1.6; 11.0)
Death	17 (0.7; 6.2)	11 (0.4; 3.0)
Invasive contralateral breast tumor	11 (0.4; 4.0)	10 (0.4; 2.7)
Invasive ipsilateral breast tumor	8 (0.3; 2.9)	9 (0.4; 2.5)

Note: Values in table are given as; n = total number of first events belonging to a particular iDFS-event (absolute number of patients in % experiencing the event; relative proportion of the event as a % of all first events

Figure 4 Relative percentage of first events, per iDFS event type



iDFS analysis by stratum and other subgroups

Subgroup analyses demonstrated consistent treatment effect across stratification factors of anatomic stage, prior (neo)adjuvant CT, menopausal status, and geographic region (8, 9).

The observed iDFS benefit across selected key subgroups are reported below, see summary Table 25. Generally, a homogeneous treatment effect was observed across strata and subgroups, see detailed reporting Appendix L in Table 104 (8, 9).

The study included N0 patients equivalent to their share in the overall target population, resulting in relatively small subgroup with only ≈ 13 % of the patients in the study. The study was not powered to claim superiority in subgroups. Although the subgroup did not reach nominal statistical significance (Table 25), there is no interaction between nodal status and efficacy with HRs and absolute differences being consistent between N0 and the ITT population. Furthermore, there are no biological rationale supporting differences in efficacy across nodal status, which is also reflected in the EMA indication covering all

high-risk eBC patients regardless of nodal status (1). It should be noted that the N0 included, is a specific high-risk group required to have T3-T4 tumors or T2 with additional high-risk features (grade 3 or grade 2 with high genomic risk). Exclusion of this group is deemed inappropriate, as the DBCG registry data clearly demonstrates these patients have an equivalent risk of recurrence, and the trial data demonstrates consistent efficacy regardless of nodal status.

Table 25 Summary of iDFS efficacy across key subgroups compared to ITT

Population	RIB + ET, %	ET, %	4-y abs. benefit, %	HR (95%CI)
ITT	88.5	83.6	4.9	0.715 (0.609–0.840)
Stage II	93.9	89.6	4.3	0.644 (0.468–0.887)
Stage III	84.3	78.4	5.9	0.737 (0.611–0.888)
Premenopausal women + men	90.7	85.3	5.4	0.677 (0.523–0.877)
Post-menopausal	86.8	82.2	4.6	0.760 (0.619–0.933)
N1-3	88.0	83.0	5.0	0.731 (0.617–0.866)
N0	92.1	87.0	5.1	0.666 (0.397–1.118)

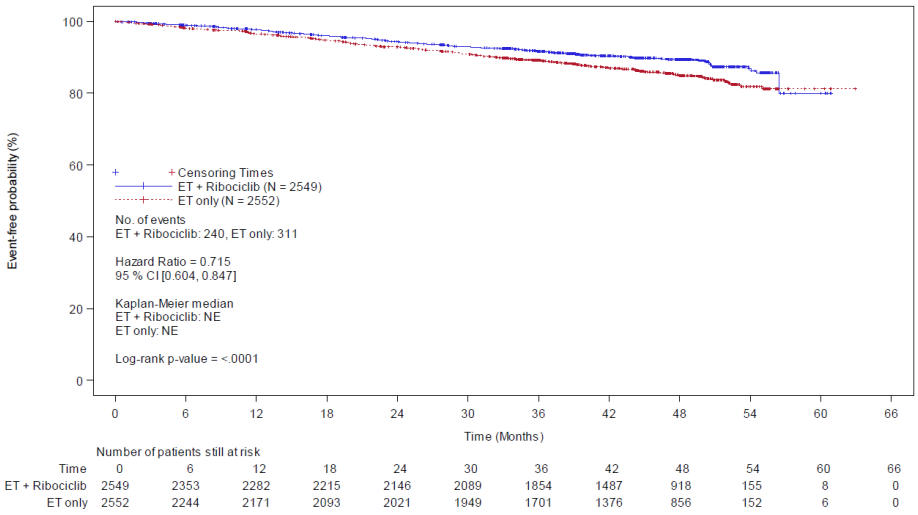
Secondary endpoint — Distant disease-free survival (DDFS)

As of the 4-year landmark analysis data cut-off date (April 29, 2024), 240 patients (9.4%) in the RIB + ET arm had a DDFS event compared with 311 patients (12.2%) in the ET only arm. A statistically significant improvement in DDFS using the STEEP criteria as per investigator assessment was demonstrated in the RIB + ET arm compared with the ET only arm (one-sided stratified log-rank test nominal P-value <0.0001). An estimated 28.5% relative reduction was observed in the risk of DDFS for patients in the RIB + ET arm (HR: 0.715, 95% CI: 0.604–0.847). The 4-year DDFS rates were 89.4% (95% CI: 88.0–90.7) in the RIB + ET arm and 84.9% (95% CI: 83.2–86.5) in the ET only arm (Figure 5). These results further translated to a 4.5% improvement in the 4-year DDFS rate in favor of ribociclib plus NSAI (7, 90). A summary of DDFS in the ITT population is shown in Table 26.

Table 26 Summary of DDFS (4-year landmark analysis): ITT (8, 9).

	RIB + ET (N=2,549)	ET only (N=2,552)
Number of events, n (%)	240 (9.4)	311 (12.2)
Hazard ratio (95% CI), p-value	0.715 (0.604–0.847), <0.0001	
DDFS rate 12 months, % (95% CI)	97.7 (97.0-98.2)	96.5 (95.7-97.2)
DDFS rate 24 months, % (95% CI)	94.4 (93.4-95.3)	92.9 (91.7-93.9)
DDFS rate 36 months, % (95% CI)	91.6 (90.4–92.7)	89.2 (87.8–90.4)
DDFS rate 48 months, % (95% CI)	89.4 (88.0–90.7)	84.9 (83.2–86.5)

Figure 5 Kaplan-Meier plot for DDFS



Abbreviations: CI: Confidence Interval; DDFS: Distant Disease-Free Survival; ET: Endocrine Therapy; NE: Not Estimable. Note: P-value from the stratified log-rank test is one-sided. Source: Novartis Data on File (4-year landmark analysis) (8, 9).

Exploratory endpoint — Distant recurrence-free survival (DRFS)

[redacted]

Table 27 Summary of DRFS (4-year landmark analysis): ITT (9)

	RIB + ET (N=2,549)	ET only (N=2,552)
[redacted]		

Figure 6 Kaplan-Meier plot for DRFS (9)

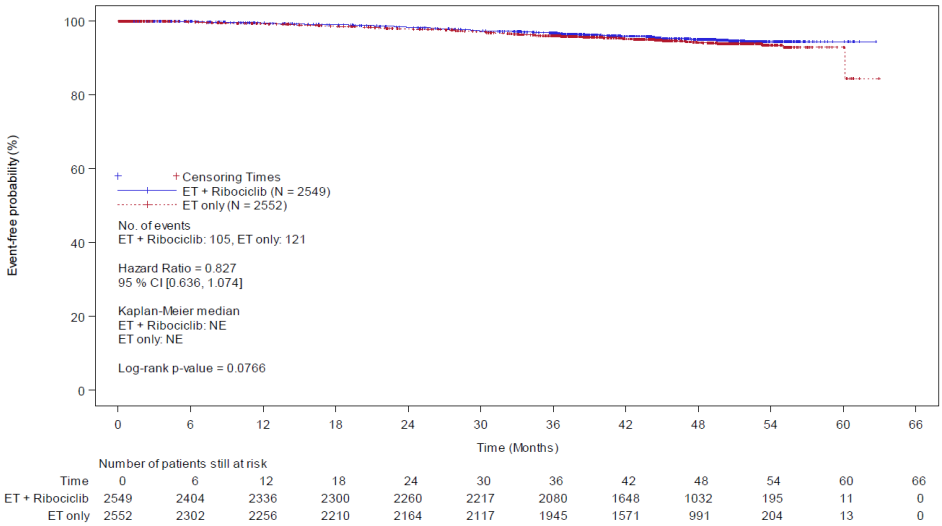
Secondary endpoint: Overall survival

As of the 4-year landmark analysis data cut-off date (April 29, 2024), the median duration of follow-up for OS was 44.3 months. OS data at the 4-year landmark analysis showed a numerically lower mortality rate in favor of RIB + ET, with a total of 105 (4.1%) events in the RIB + ET arm and 121 (4.7%) in the ET only arm (one-sided stratified log-rank test nominal P-value=0.0766). A positive trend for OS was observed among patients in the RIB + ET arm. The OS HR for the RIB + ET arm vs. the ET only arm was 0.827 (95% CI: 0.636−1.074). The 4-year OS rates were 95.0% (95% CI: 94.0−95.9) in the RIB + ET arm and 94.2% (95% CI: 93.0−95.2) in the ET only arm, reflecting a 0.8% absolute benefit favoring RIB + ET. A summary of OS in the ITT population at the time of the 4-year landmark analysis is shown in Table 28 (8, 9). Patients will be followed 91 months according to protocol (7.6 years) for further analyses.

Table 28 Summary of OS (4-year landmark analysis): ITT (8, 9)

	RIB + ET (N=2,549)	ET only (N=2,552)
Number of events, n (%)	105 (4.1)	121 (4.7)
Hazard ratio (95% CI), p value	0.827 (0.636–1.074), p = 0.0766	
OS-rate 12 months, % (95 CI)	99.5 (99.2–99.7)	99.3 (98.9–99.6)
OS-rate 24 months, % (95 CI)	98.3 (97.7–98.8)	97.9 (97.2–98.4)
OS-rate 36 months, % (95 CI)	96.8 (96.0–97.5)	96.0 (95.1–96.8)
OS-rate 48 months, % (95 CI)	95.0 (94.0–95.9)	94.2 (93.0–95.2)

Figure 7 Kaplan-Meier plot for OS



Abbreviations: CI: Confidence Interval; ET: Endocrine Therapy; NE: Not Estimable; OS: Overall Survival. Note: p-value from the stratified log-rank test is one-sided. Source: Novartis Data on File (4-year landmark analysis) (8, 9).

Summary of clinical efficacy

In summary, robust, statistically significant and clinical meaningful improvements were documented for all efficacy outcomes; iDFS, DDFS and DRFS. These changes improved over time with absolute benefit increasing from 3-year to 4-year landmark analysis based on iDFS/DDFS/DRFS rates. This highlights the sustained efficacy after all patients stopped ribociclib treatment with no evidence of treatment waning. Further, the iDFS analysis conducted in all relevant subgroups substantiates the need to treat the full ITT population, as no statistical or clinical meaningful differences were noted.

Notably, the differences in iDFS/DDFS/DRFS rates were predominantly driven by a reduction of distant recurrences which are considered incurable (see section 6.1.4, Table 24). Although no mature data is available on OS, iDFS has been thoroughly validated as a robust surrogate for OS (section 3.7.1). The primary shortcoming with OS in adjuvant BC trials is the fact, that it is anticipated to take up to a decade to mature, making it infeasible as a primary outcome. Given the shortcoming with acquiring mature OS data, the large and consistent reductions in iDFS across subgroups should be considered sufficient to document the overall benefit of adding ribociclib to existing ET, with the reassurance of a nominal improvement in OS observed.

7. Comparative analyses of efficacy

This section is not relevant, as the documentation rely on the NATALEE trial, a head-to-head study directly comparing the RIB + ET vs. the comparator consisting of ET.

7.1.1 Differences in definitions of outcomes between studies

Not relevant

7.1.2 Method of synthesis

Not relevant

7.1.3 Results from the comparative analysis

Not relevant

7.1.4 Efficacy – results per [outcome measure]

Not relevant

8. Modelling of efficacy in the health economic analysis

The IDFS curve from the NATALEE trial has been used as the main source of efficacy data in the health economic model. Survival distributions were estimated to the IDFS curve and patients were distributed to health states according to type of event as described in section 4.2. For a complete overview of the methods for extrapolation, please refer to Appendix D.

8.1 Presentation of efficacy data from the clinical documentation used in the model

8.1.1 Extrapolation of efficacy data

See below

8.1.1.1 Extrapolation of IDFS

The statistical tests of proportional hazards did not allow for the rejection of proportionality. However, an argument could be made for not-proportionality and thus individual curve fittings have been used. The same parameterization curve (gamma) was chosen for both arms. Additionally, a treatment effect waning was applied to the RIB + ET arm, adjusting the curve so it would follow the same function as the ET only arm after a set period. The treatment effect waning time was chosen to initiate at 8 years and last until background mortality and IDFS became equal on the basis of the assessment of abemaciclib by the DMC (28). A detailed explanation of the choices is presented in Appendix D. The extrapolation of the chosen curve on a 10-year timeline is presented below in Figure 8.

Figure 8 Selected extrapolation and Kaplan-Meier of RIB + ET and ET only in the base case analysis

I: Individual; K-M: Kaplan Meier

Table 29 Summary of assumptions associated with extrapolation of iDFS

Method/approach	Description/assumption
Data input	NATALEE
Model	Full parameterization and cubic spline models
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	[redacted]
Function with best BIC fit	[redacted]
Function with best visual fit	[redacted]
Function with best fit according to evaluation of smoothed hazard assumptions	RIB + ET: NA ET only: NA
Validation of selected extrapolated curves (external evidence)	NA
Function with the best fit according to external evidence	RIB + ET: NA ET only: NA
Selected parametric function in base case analysis	[redacted]

Method/approach	Description/assumption
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	Yes. The waning effect is assumed to begin 8 years after treatment initiation with waning lasting until the background mortality and IDFS are the same, as per the DMC assessment of abemaciclib
Assumptions of cure point	No

8.1.2 Calculation of transition probabilities

8.1.2.1 Non-Metastatic Recurrence and Remission States

Transition probabilities from the NMR state to death were assumed to be the same as the probability of death for the general population using the probability of death estimated from the iDFS curve as a floor. Patients who remain alive in the NMR state for a year transition to the remission state. The probability of death in the remission state was similarly assumed to be equal to that of the general population using the IDFS probability of death as a floor.

The use of IDFS as a floor for these two health states was programmed as a modelling option and was selected in the base case as to not overestimate effectiveness. The probability of distant recurrence within the remission state was estimated consistently with that in TA810 NICE appraisal of abemaciclib (46). The primary source for this parameter was NICE TA632 of trastuzumab, which used a published study of 12,836 eBC patients and estimated the risk of the incidence of a second malignancy after receipt of adjuvant therapy (47). The monthly transition probability of 0.0076 was calculated from the mean time until progression of 7.6 years (48).

Table 30 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Non-metastatic recurrence	Remission	NICE HTA	TA632 (47)

8.2 Presentation of efficacy data from other sources

The data used to inform the parameterization for the PFS and OS curve in the ET-resistant and ET-sensitive substates was based on the latest DCOs of MONALEESA-2 and MONALEESA-3 (June 2021 and January 2022, respectively). Further, an ITC was conducted to inform hazard ratios between potential treatment options in these two treatment settings of HR+/HER2- aBC. The choice of included studies is further detailed in Appendix D.

8.3 Modelling effects of subsequent treatments

The effects of the subsequent treatments are modelled as a PSM within the semi-continuous Markov cohort model. The PSMs use extrapolated event data for PFS and OS from MONALEESA-2 and MONALEESA-3, which is weighted with HRs calculated from an ITC. The included treatment alternatives were based on input from Canadian KOLs, which informed an ITC of the included alternatives, where details can be found in Appendix D. The weighting for the local adaption was based on Danish KOL opinion and DMC assessment of abemaciclib.

8.4 Other assumptions regarding efficacy in the model

N/A

8.5 Overview of modelled average treatment length and time in model health state

Table 31 outlines the average modelled treatment length for RIB + ET and ET only. The former is based on KM curves observed in the trial, whereas the latter is derived from an extrapolated curve. However, the cost pertaining to the ET treatment constitutes a fraction of the cost of CDK 4/6 and has no great impact on the results of the model. It should be noted there is a large difference between the observed and modelled average TTD for the ET treatment. This is due to the lack of follow-up, as all patients has not been in the trial for 5 years at the DCO.

Table 31 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

	Modelled average TTD	Observed average from relevant study: NATALEE
Ribociclib	[redacted]	[redacted]
ET for RIB + ET only arm	48.02 months	39.6 months
ET only	46.26 months	38.2 months

ET: Endocrine therapy; ToT: Time on treatment

9. Safety

9.1 Safety data from the clinical documentation

The Safety set included all randomized patients who received any study treatment (i.e., at least one dose of ribociclib or ET). Patients were analyzed according to the study treatment received.

Table 32 presents safety data from the 29 April 2024 data cut-off (4-year landmark analysis, data-on-file (9), where the safety set comprised 2,529 patients in the RIB + ET arm and 2,441 patients in the ET only arm. The data aligns with previously reported safety data from the final iDFS analysis (6). The safety profile of ribociclib remained stable and predictable, with no new safety signals identified over the follow-up for the overall study of 49.6 months as of 29 April 2024, when all patients were reported to be off ribociclib.

Overall, 98.1% of patients in the RIB + ET arm and 88.3% of patients in the ET only arm experienced at least one AE during the study, but all AEs were well characterized and readily identifiable with prescheduled laboratory work or physical examination and manageable with appropriate interventions. An overview of the SAEs reported in the NATALEE trial is presented in Appendix E and as seen, there were slightly more SAEs of all grades reported in the RIB + ET arm (14.8%) compared to the ET only arm (10.9%), however, all SAEs had an incidence of $<$ 1% in both arms and in total, 2.8% in the RIB + ET arm compared with 0.5% in the ET only arm had SAEs that were considered to be related to study treatment.

Rates of ribociclib discontinuation due to AEs remained stable through all the data cuts, with a < 1.0% increase from the previous cut-off. 20.0% of patients discontinued ribociclib treatment in the RIB + ET arm and 4.9% discontinued NSAI in the ET only arm due to AEs. 5.3% discontinued NSAI in the RIB + ET arm due to AEs. The most reported AEs (in ≥ 10 patients) leading to study drug discontinuation in the RIB + ET arm were ALT increased (7.2%), AST increased (2.9%), arthralgia (1.3%), neutropenia (0.8%), fatigue (0.8%), nausea (0.5%), and asthenia (0.5%). The most reported AE leading to study treatment discontinuation in the ET only arm was arthralgia (2.1%). Grade 3−5 AEs leading to study treatment discontinuation were reported in approximately 9.9% of patients in the RIB + ET arm and in approximately 1.8% of patients in the ET only arm.

An overview of the most common grade 3-5 AEs is presented in Appendix 0. The most common grade ≥ 3 AEs (with an incidence ≥ 1%), irrespective of causality, in the RIB + ET group were presented by AEs related to moderate laboratory abnormalities such as neutropenia (28.1%), neutrophil count decreased (17.7%), ALT increased (7.7%), AST increased (4.6%), white blood cell (WBC) decreased (3.8%), leukopenia (3.7%), and hypertension (2.3%). The most frequently reported grade 3 AE, irrespective of causality, in the ET only group was hypertension (2.3%). The majority of grade ≥ 3 AEs in the RIB + ET group are consistent with the known safety profile of ribociclib established in mBC (please see Appendix 0), presented predominantly by events pertaining to the known risk of myelosuppression. The events occur early during treatment, usually within the first few cycles of therapy, and their incidence does not increase over time. Notably, the clinical impact of the grade ≥ 3 TEAEs on patients in the RIB + ET group was limited, as most events were asymptomatic laboratory findings and completely resolved with appropriate management as per protocol (6). Importantly, the addition of ribociclib to ET did not impact tolerability to ET, as demonstrated by the similar discontinuation rates of ET due to AE in both treatment groups. Also, as shown in section 9.1, which presents the results on HRQoL from the NATALEE trial, the higher incidences of AEs and SAEs reported in the RIB + ET arm compared to the ET only arm did not impact patient's HRQoL as demonstrated by the similar HRQoL reported in both treatment arms in the NATALEE trial

and were primarily laboratory findings. Similarly to the monarchE study HRQoL data was not collected before 3 months into the treatment, which did DMC critiqued during the assessment of abemaciclib, as many AEs occur during the first months after initiation of therapy (28). Although the critique of the timing of the measurements is considered valid the impact is minimal as AEs associated with ribociclib are overwhelmingly asymptomatic laboratory findings associated with myelosuppression.

Of importance, compared with data from the MONALEESA studies using the 600-mg dose in the advanced setting, the starting dose of 400 mg of ribociclib in the adjuvant setting was associated with lower rates of dose-dependent neutropenia as well as QTc-prolongations (89). The neutropenia grade ≥ 3 and all grades were 44.4% and 62.8% in NATALEE vs. 60.0% and 74.0% in the MONALESSA trials pooled (9, 89), when using a grouped term that combines AEs reported as neutropenia or neutrophil count decreased. ECG QT-prolongation reported as grade ≥ 3 and all grades were reported for 0.2% and 4.2% of patients in NATALEE vs. 1.2% and 6.5% of patients in the MONALESSA trials pooled (9, 89).

At the 4-year landmark analysis, 687 patients (27.2%) in the RIB + ET group had a ribociclib dose reduction and 23.0% had the dose reduced due to AEs. The dose reductions in the RIB + ET group were largely mandated by protocol guidance for dose adjustment, and most AEs were not associated with clinical symptoms or manifestations and were generally reversible upon treatment adjustment. Importantly, patients with and without dose reductions had an identical median duration of RIB exposure of 35.7 months, indicating dose reductions allows the patients to stay on treatment (91). In addition, iDFS analysis based on relative dosing intensity strata (Low RDI = 0% to <82.27%. b Medium RDI = 82.27% to <97.44%. c High RDI = ≥97.44%) did not reveal any difference in efficacy strongly suggesting it is safe and appropriate to reduce the dose to 200 mg/day to allow patients to stay on ribociclib, managing AEs without compromising efficacy (91).

In the ET only group, dose interruptions of NSAI were reported, and 46.7% in the RIB + ET group and 36.8% in the ET only group had NSAI dose interruptions. 11.6% and 5.7% in the RIB + ET group and the ET only group had their dose interrupted due to AEs.

Table 32 Overview of safety events in the NATALEE trial.

	RIB +ET (N=2,526) (data on file)	ET only (N=2,441) (data on file)	Difference, % (95 % CI)
Number of adverse events, n	NR	NR	NR
Number and proportion of patients with ≥ 1 adverse events, n (%)	2,478 (98.1)	2,155 (88.3)	9.8% (8.4%, 11.2%)
Number of serious adverse events, n	NR	NR	NR
Number and proportion of patients with ≥ 1 serious adverse events, n (%)	375 (14.8)	267 (10.9)	3.9% (2.0%, 5.8%)

	RIB +ET (N=2,526) (data on file)	ET only (N=2,441) (data on file)	Difference, % (95 % CI)
Number of CTCAE grade ≥ 3 events, n*	NR	NR	NR
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events, n (%)	1,622 (64.2)	481 (19.7)	44.5% (42.1%, 47.0%)
Number of adverse reactions, n	NR	NR	NR
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	NR	NR	NR
Number and proportion of patients who had a dose reduction, n (%)	All causes: 687 (27.2) Due to AEs: 582 (23.0)	NR	NR
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	732 (28.7)	813 (31.9)	-3.1% (-5.7%, -0.6%)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	Ribociclib: 509 (20.0%) NSAI: 5.3%	NSAI: 124 (4.9%)	15.1% (13.3%, 16.9%)

*Only AEs with at least 1% incidence in either arm was counted in this analysis.

No SAEs occurred with a frequency of ≥ 5% in either treatment arm at the 29 April 2024 cut-off and therefore, Table 33 has not been filled out. A list of all SAEs observed in the safety set in the NATALEE trial is presented in Appendix E.

Table 33 Serious adverse events with a frequency of ≥5% in either treatment arm

Adverse events	ET + Ribociclib (N=2,526) (data on file)		ET only (N=2,441) (data on file)	
	Number of patients with adverse events	**Number of adverse events**	**Number of patients with adverse events**	**Number of adverse events**
Adverse event, n (%)	N/A	N/A	N/A	N/A

Table 34 presents the adverse events used in the health economic model. The rationale for including the adverse events presented in the table was more than 5% experienced the grade ≥ 3 in either arm.

Table 34 Adverse events used in the health economic model

Adverse events	Frequency (%) Intervention	Frequency (%) Comparator	Source	Justification
Increased Alanine aminotransferase	7.68 %	0.70 %	NATALEE	More than 5% experienced grade 3 in either arm
Neutropenia	28.11 %	0.57 %	NATALEE	More than 5% experienced grade 3 in either arm

9.2 Safety data from external literature applied in the health economic model

No safety data was used from external source.

10. Documentation of health-related quality of life (HRQoL)

For PRO data, we refer to data recently published and partly use data-on-file from the second interim analysis with data cut-off 11 January 2023 (27.7-month median follow-up) (10, 51). No updated PRO data is not available as part of the final or 4-year landmark iDFS analysis, comprising of an efficacy analysis and safety update.

In the following, results are presented on the physical functioning sub-scale score of the EORTC QLQ-C30 which was the primary PRO variable of interest in the NATALEE trial, and the VAS scores of the EQ-5D-5L, which was a secondary PRO variable of interest in the trial.

The EORTC QLQ-C30 questionnaire is a 30-item questionnaire composed of 5 multi-item scales (physical, role, social, emotional and cognitive functioning) three symptom scales (fatigue, pain, and nausea and vomiting), and a global health and quality-of-life scale. The remaining single items assess additional symptoms commonly reported by cancer patients (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea), as well as the perceived financial impact of the disease and treatment (92). Based on 30 questions in total, the scores range from 0 to 100. Version 3.0 of the QLQ-C30 differs from other versions in that it has four-point scales for the first five items. A high score on functional domains represents a high level of functioning.

The EQ-5D is a questionnaire with 5 questions, where subjects are asked to indicate their health state at the time of survey by ticking the box next to the most appropriate statement in each of the five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression that each has three levels (no problem,

moderate problem, severe problem). In addition, a health state assessment is made using a visual analogue scale (VAS) that records the respondent's self-rated health on a 100 mm (or 100 point) vertical VAS, where the endpoints are labelled "Best imaginable health state" (= 100) and "Worst imaginable health state" (= 0). The number and percentage of subjects in each of the 3 categories for each question was presented by visit up to the study end for each treatment group.

Both the EORTC QLQ-C30 and EQ-5D-5L are recognized as reliable and valid measures frequently used in clinical studies of patients with BC (92-94).

Table 35 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	NATALEE trial	Used to derive utilities for the health economic model
EORTC QLQ-C30 version 3.0	NATALEE trial	Used to assess clinical effectiveness in terms of improving HRQoL

At the 11 January 2023 data cut-off, overall completion rates for the PRO questionnaires during the treatment period were comparable between both treatment arms (10). Data were categorized as fully completed, partially completed (defined as ≥ 1 item completed, but not all items completed), or not completed based on extent of completion of the questionnaires. At baseline, PRO data was collected from 2,495 patients (97.9%) in the RIB + ET arm vs. 2,483 patients (97.3%) in the ET only arm ('expected to complete' in the table below). Among those patients with baseline PRO data, 84.53% of patients in the RIB + ET arm partially completed compared to 84.13% in the ET only arm, 15.47% of the patients in the RIB + ET arm fully completed compared to 15.87% in the ET only arm. There were no non-completions in either treatment arm at baseline. As of the data cut-off date of 11 January 2023, out of 544 patients with completed EOT visit, data was collected for 469 (86.2%) in the RIB + ET arm compared to 502 out of 610 patients (82.3%) in the ET only arm. Of those patients with EOT PRO data, 67.65% of patients in the RIB + ET arm partially completed compared to 68.20% in the ET only arm, 18.57% of the patients in the RIB + ET arm fully completed compared to 14.10% in the ET only arm. 13.8% of patients in the RIB + ET arm did not complete compared to 17.7% in the ET only arm.

Table 36 Pattern of missing data and completion of PRO (FAS population, 11 January 2023 cut-off). Source: (10).

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)	
	Number of patients at randomization	**Number of patients for whom data is missing (% of patients at randomization)***	**Number of patients "at risk" at time point X**	**Number of patients who completed (% of patients expected to complete)**	
				Fully completed	**Partially completed**

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)	
Baseline	RIB + ET: 2,549 ET only: 2,552	RIB + ET: 54 (2.12%) ET only: 69 (2.70%)	RIB + ET: 2,495 ET only: 2,483	RIB + ET: 386 (15.47%) ET only: 394 (15.87%)	RIB + ET: 2,109 (84.53%) ET only: 2,089 (84.13%)
Week 13 Day 1/C4D1	RIB + ET: 2,549 ET only: 2,552	RIB + ET: 270 (10.59%) ET only: 403 (15.79%)	RIB + ET: 2,353 ET only: 2,218	RIB + ET: 402 (17.08%) ET only: 297 (13.39%)	RIB + ET: 1,877 (79.77%) ET only: 1,852 (83.50%)
Week 25 Day 1/C7D1	RIB + ET: 2,549 ET only: 2,552	RIB + ET: 345 (13.53%) ET only: 473 (18.53%)	RIB + ET: 2,294 ET only: 2,159	RIB + ET: 485 (21.14%) ET only: 327 (15.15%)	RIB + ET: 1,719 (74.93%) ET only: 1,752 (81.15%)
Week 37 Day 1/C10D1	RIB + ET: 2,549 ET only: 2,552	RIB + ET: 331 (12.99%) ET only: 475 (18.61%)	RIB + ET: 2,268 ET only: 2,147	RIB + ET: 586 (25.84%) ET only: 373 (17.37%)	RIB + ET: 1,632 (71.96%) ET only: 1,704 (79.37%)
Week 49 Day 1/C13D1	RIB + ET: 2,549 ET only: 2,552	RIB + ET: 367 (14.39%) ET only: 479 (18.77%)	RIB + ET: 2,227 ET only: 2,125	RIB + ET: 603 (27.08%) ET only: 394 (18.54%)	RIB + ET: 1,579 (70.90%) ET only: 1,679 (79.01%)
Week 61 Day 1/C16D1	RIB + ET: 2,549 ET only: 2,552	RIB + ET: 379 (14.87%) ET only: 524 (20.53%)	RIB + ET: 2,211 ET only: 2,072	RIB + ET: 569 (25.73%) ET only: 404 (19.50%)	RIB + ET: 1,601 (72.41%) ET only: 1,624 (78.38%)
Week 73 Day 1/C19D1	RIB + ET: 2,549 ET only: 2,552	RIB + ET: 413 (16.20%) ET only: 552 (21.63%)	RIB + ET: 2,173 ET only: 2,039	RIB + ET: 558 (25.68%) ET only: 403 (19.76%)	RIB + ET: 1,578 (72.62%) ET only: 1,597 (78.32%)
Week 85 Day 1/C22D1	RIB + ET: 2,549 ET only: 2,552	RIB + ET: 456 (17.89%) ET only: 590 (23.12%)	RIB + ET: 2,145 ET only: 1,997	RIB + ET: 570 (26.57%) ET only: 414 (20.73%)	RIB + ET: 1,523 (71.00%)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)	
					ET only: 1,548 (77.52%)
Week 97 Day 1/C25D1	RIB + ET: 2,549 ET only: 2,552	RIB + ET: 602 (23.62%) ET only: 743 (29.11%)	RIB + ET: 1,990 ET only: 1,849	RIB + ET: 506 (25.43%) ET only: 367 (19.85%)	RIB + ET: 1,441 (72.41%) ET only: 1,442 (77.99%)
Week 121 Day 1/C31D1	RIB + ET: 2,549 ET only: 2,552	RIB + ET: 954 (37.42%) ET only: 1027 (40.24%)	RIB + ET: 1,659 ET only: 1,566	RIB + ET: 418 (25.20%) ET only: 286 (18.26%)	RIB + ET: 1,177 (70.95%) ET only: 1,239 (79.12%)
Week 145 Day 1/C37D1	RIB + ET: 2,549 ET only: 2,552	RIB + ET: 1492 (58.53%) ET only: 1555 (60.93%)	RIB + ET: 1,085 ET only: 1,025	RIB + ET: 257 (23.69%) ET only: 189 (18.44%)	RIB + ET: 800 (73.73%) ET only: 808 (78.83%)
Week 169 Day 1/C43D1	RIB + ET: 2,549 ET only: 2,552	RIB + ET: 2304 (90.38%) ET only: 2306 (90.36%)	RIB + ET: 262 ET only: 265	RIB + ET: 48 (18.32%) ET only: 43 (16.23%)	RIB + ET: 197 (75.19%) ET only: 203 (76.60%)
End of Treatment (EOT)	RIB + ET: 2,549 ET only: 2,552	RIB + ET: 2080 (80.16%) ET only: 2050 (80.33%)	RIB + ET: 544 ET only: 610	RIB + ET: 101 (18.57%) ET only: 86 (14.10%)	RIB + ET: 368 (67.65%) ET only: 416 (68.20%)

*Percentages represent the percentage missing compared to patients at randomization and not percentages of "expected to complete" to be aligned with the DMC template.

10.1 Presentation of the health-related quality of life measured with the EORTC QLQ-C30 questionnaire

10.1.1 Study design and measuring instrument

Based on the experience from all clinical trials testing CDK4/6 in breast cancer patients (mainly aBC), the quality of life have been reported to be stable when adding CDK4/6 to ET with some evidence suggesting greater pain reduction in the experimental arms with CDK4/6 (95). The a priori expectation to changes in the PRO associated with the add-on of ribociclib to ET is for HRQoL to either remain stable or slightly improve. This is based on the potential for new treatments to more effectively target cancer cells, thereby reducing the physical and psychological burden of breast cancer. Enhanced efficacy could lead to

better disease control and fewer symptoms, which contribute to improved overall well-being and HRQoL. On the other hand, adding any additional treatment to an existing treatment paradigm will cause some level of additional toxicity. Additionally, improved physical functioning and reduced fatigue or pain could be hypothesized, as new treatments may alleviate some of the debilitating symptoms of breast cancer and its treatment.

10.1.2 Data collection

Please see Table 36. Scoring of raw data and methods for handling of missing items or missing assessments were handled according to scoring manuals. No formal statistical tests were performed on PRO data and hence no multiplicity adjustment was applied.

10.1.3 HRQoL results

In general, the EORTC QLQ-C30 physical functioning of patients treated with RIB + ET was similar to that of patients treated with ET only (10). Mean baseline physical functioning scores from the EORTC QLQ-C30 were well balanced between the treatment arms: 85.0 (on a scale of 0 to 100) in both the RIB + ET and ET only arms (10). Physical functioning scores were generally similar between the two treatment arms throughout the study, with no meaningful differences at any post-baseline timepoint through to EOT. There was a slight decline in physical functioning (i.e., decrease) in scores for patients in both treatment arms post-baseline (10). Overall, treatment with RIB + ET maintained HRQoL scores over time, further supporting the clinical benefit of the treatment regimen in the target population. The mean changes from baseline at various time points are presented in Figure 9 and Table 37.

Figure 9 Change from baseline in Physical Functioning Score of EORTC QLQ-C30 Questionnaire (FAS). Source: data on file.

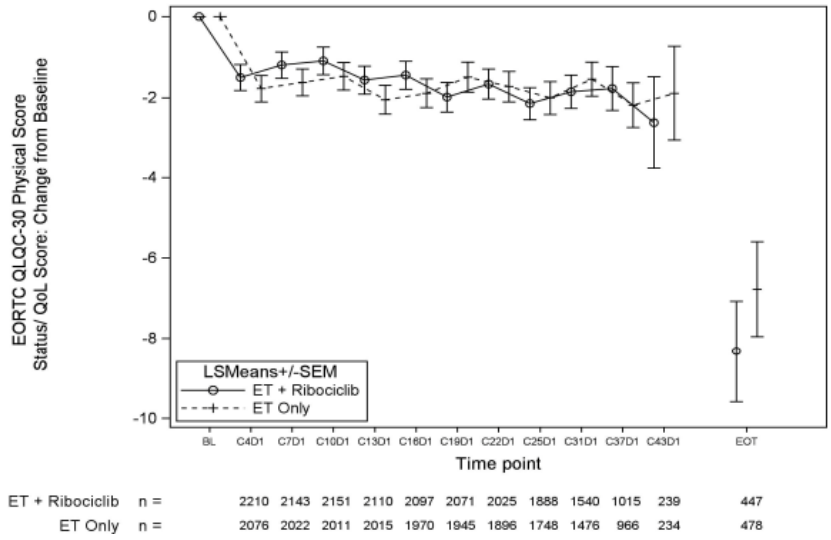


Figure note: The time profile provides the average estimates for the change from baseline for the interval from baseline up to the respective cycle as estimated from general linear model (GLM) adjusted by stratification factors at randomization. Time Point: See table below for explanation.

Table 37 Physical functioning score of EORTC QLQ-C30 (FAS) summary statistics. Source: (10, 51). P-values are nominal with no adjustments for multiplicity

	RIB + ET		ET only		RIB + ET Vs. ET only
	N	**Mean (SE)**	**N**	**Mean (SE)**	**Difference (95% CI) p-value**
Baseline (BL)	2,475	84.99 SD: 14.87 SE: 0.299	2,465	84.99 SD: 14.87 SE: 0.300	0.00 (-0.830, 0.830, p = 1.000)
[redacted]					
[redacted]					
[redacted]					
[redacted]					

	RIB + ET		ET only		RIB + ET Vs. ET only
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

10.2 Presentation of the health-related quality of life measured with the EQ-5D-5L

10.2.1 Study design and measuring instrument

See section 10.2.1.

10.2.2 Data collection

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

the patient. The number and proportion of patients who have completed the EQ-5D VAS at each time point are presented in Table 36.

Scoring of raw data and methods for handling of missing items or missing assessments were handled according to scoring manuals for each respective patient questionnaire. No formal statistical tests were performed on PRO data and hence no multiplicity adjustment was applied.

10.2.3 HRQoL results

In general, the EQ-5D VAS of patients treated with RIB + ET was similar to that of patients treated with ET only (51). Mean baseline VAS scores were well balanced between the treatment arms: 78.33 in the RIB + ET arm and 78.05 in the ET only arm (on a scale of 0 to 100). The VAS scores were generally similar between the two treatment arms throughout the study, with no meaningful differences at any post-baseline timepoint through to the EOT. Overall, treatment with RIB + ET maintained HRQoL scores over time, further supporting the clinical benefit of the treatment regimen in the target population. The mean change from baseline at various time points are presented in Figure 10 and Table 38.

Figure 10 Change from baseline in VAS EQ-5D-5L. Source: data on file.

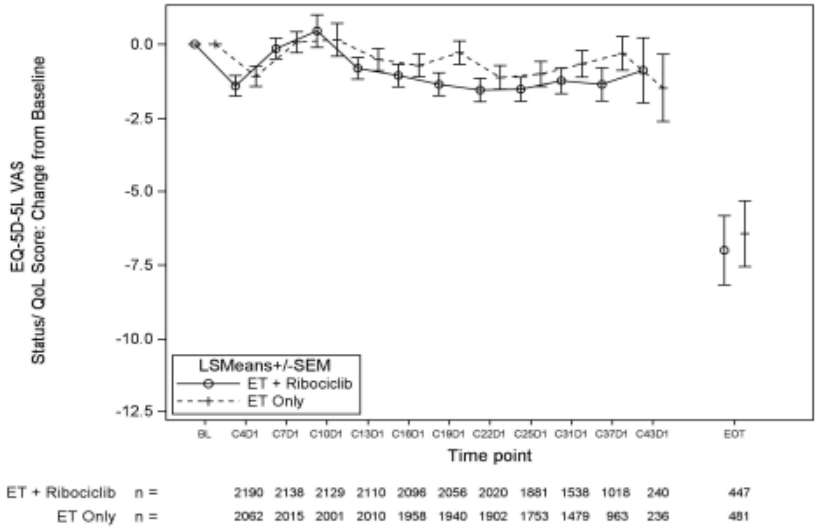


Figure note: The time profile provides the average estimates for the change from baseline for the interval from baseline up to the respective cycle as estimated from general linear model (GLM) adjusted by stratification factors at randomization. Time Point: BL = Baseline, C4D1 = Week 13 Day 1, C7D1 = Week 25 Day 1, C10D1 = Week 37 Day 1, C13D1 = Week 49 Day 1, C16D1 = Week 61 Day 1, C19D1 = Week 73 Day 1, C22D1 = Week 85 Day 1, C25D1 = Week 97 Day 1, C31D1 = Week 121 Day 1, C37D1 = Week 145 Day 1, C43D1 = Week 169 Day 1, 14 = End of Treatment.

Table 38 VAS EQ-5D-5L (FAS population) summary statistics. P-values are nominal with no adjustments for multiplicity. Source: data on file (51).

	RIB + ET		ET only		RIB + ET Vs. ET only
	N	**Mean (SE)**	**N**	**Mean (SE)**	**Difference (95% CI) p-value**
Baseline	2,473	78.33 SE: 0.300	2,466	78.05 SE: 0.304	-0.28 (-1.117, 0.557, p = 0.512)
[redacted]					

10.3 Health state utility values (HSUVs) used in the health economic model

10.3.1 HSUV calculation

In the base case, dimension scores for the 5 domains of the EQ-5D-5L assessments collected in NATALEE were converted to index utility scores with Danish preference weights from Jensen et al. 2021 in accordance with DMC methods (96).

For each study subject, utility index scores at each assessment were classified into health states based on recorded event times and types for IDFS and OS. Assessments in IDFS were further classified by randomized treatment group and on-treatment versus off-treatment: assessments in IDFS prior to treatment discontinuation were classified as on-treatment and those in IDFS after discontinuation were classified as off-treatment. Numbers of patients and the numbers of valid utility assessments were reported by time since the screening visit per the assessment scheduled and by health state (i.e., each patient can contribute multiple assessments to a given health state). Numbers of patients and EQ-5D-5L assessments by health state are shown in Table 39.

Table 39 Numbers of patients and assessments contributing to generalized estimating equations (GEE) Regression Analyses of EQ-5D-5L assessments for patients in NATALEE. Source: Novartis data on file.

Health State	Assessments	Patients
IDFS, RIB + ET arm	24,938	2,373
IDFS, ET arm	23,389	2,259
IDFS On-Treatment, RIB + ET arm	24,281	2,339
IDFS On-Treatment, ET arm	22,644	2,217
IDFS Off-Treatment	1,402	455
Post-Recurrence (i.e., any reason)	1,311	449
Secondary Primary Malignancy	288	63
Non-Metastatic Recurrence	174	60
Distant Recurrence	849	333

EQ-5D-5L index scores were analyzed using GEEs regression (an extension of generalized linear model regression for analyzing data with correlation of the dependent variable across observations) to obtain utility values for model health states controlling for EQ-5D index values at baseline. Patients could contribute multiple observations to the analysis. To be included in the analysis, patients must have had a baseline assessment and at least one post-baseline assessment. Covariates used in the regressions were selected to correspond to health states in the health economic model. The regression included covariates to estimate utility values for the following mutually exclusive health states:

- IDFS on-treatment with RIB + ET; IDFS on-treatment with ET; IDFS off-treatment; NMR; SPM; and DR.

GEE regressions were conducted using the SAS PROC GENMOD procedure with the REPEATED statement. An autoregressive correlation structure was chosen consistent with the approach outlined in Cui 2007 (97).

Four different models were considered with different combinations of covariates (Table 40). Model 1 included an intercept term and a covariate for baseline utility value, a covariate for assessments post-disease recurrence, and a covariate for treatment arm. Models 2 and 4 included an additional covariate for on-treatment (i.e., as opposed to off-treatment) in IDFS. Models 3 and 4 included additional covariates controlling for type of

recurrence (i.e., SPM, NMR, and DR). The mean baseline EQ-5D-5L value based on DK tariffs was estimated to [redacted].

Table 40 Regression models for analyzing health state utilities in NATALEE

Model	Inter-cept	Baseline Utility	IDFS (R+ET)	IDFS (ET)	IDFS Off-Tx	IDFS On-Tx (R+ET)	IDFS On-Tx (ET)	PR	NMR	SPM	DR
1	√	√	√	√				√			
2	√	√			√	√	√	√			
3	√	√	√	√	√				√	√	√
4	√	√			√	√	√		√	√	√

R+ET: RIB + ET; ET: Endocrine therapy; IDFS: Invasive disease-free survival; Tx: Treatment; PR: Post-recurrence; NMR: Non-metastatic recurrence; SPM: Secondary primary malignancy; DR: Distant recurrence.

While the QIC statistic suggests that Model 1 had the best fit (QIC = 49,705.61), this model did not include covariates for each type of recurrence (i.e., it assumes the same utility value for SPM, non-metastatic, and distant recurrences). For the health economic model, it was preferred to use a regression model that provided separate utility estimates for each of the mutually exclusive health states in the Markov model. As such, Model 4 was chosen for use in the base case. Model 4 provided estimated health state utilities controlling IDFS by treatment arm, on-treatment versus off-treatment, DR, SPM, and NMR. In the health economic model, baseline health-state utilities in IDFS were assumed to be the same for both treatments, with the estimated utility for the ET arm as a referent, which were then adjusted to account for the impacts of AEs on QALYs by combining estimates of the utility value for IDFS on-treatment with estimates of the utility decrements associated with AEs, the difference in incidence of AEs relative to the referent (i.e., ET), and the expected duration of AEs. Estimated health state utilities used in the base case for the evaluation of the ITT population are shown in Table 41.

In the base case for the ITT population, health state utilities in IDFS while on treatment were derived based on the estimated utility for ET alone from the GEE regression (0.8335 for ITT population) and applying an age-category utility adjustment as per DMC guidelines from the general Danish population. Health state utilities for patients remaining in IDFS after discontinuing treatment and for those in the NMR state were [redacted], respectively, based on analyses of NATALEE. Utilities for patients in remission were assumed to be the same as for the general population.

10.3.1.1 Mapping

No mapping has been applied.

10.3.2 Disutility calculation

Disutilities for AEs were included as a modelling option for each treatment. When selected, this modelling option applies an AE specific utility decrement to each treatment by combining the assumed AE disutilities, their incidence, and duration. It was assumed that

all AEs considered in the model had a duration of one month. The disutility values were based on the technology assessment of abemaciclib by NICE in the UK (46).

The model includes the ability to select a referent comparator for a base utility and AE rate, upon which adjustments are applied based on differences in AEs and the inputs related to AE disutility. In the base case analysis, ET was chosen as the referent group as it has a lower side-effect profile than RIB + ET. Thus, for patients receiving ET, mean utility values for on-treatment IDFS generated from NATALEE data were assumed to innately capture the effects of AEs on HRQoL. As such, no other adjustments for AE disutilities were included for this comparator to avoid double-counting. Utilities for patients in remission were assumed to be the same as for the general population. Utility values for the PFS substates of the DR ET-resistant and DR ET-sensitive PSMs were assumed to both equal [redacted] (i.e., as estimated from NATALEE). However, as information regarding subsequent progressions after metastatic recurrence was not captured in NATALEE, utilities for DR PPS could not be directly estimated. Therefore, relative decreases between PFS and PPS utilities observed in MONALEESA-3 and MONALEESA-2 were applied to the ET-Resistant and ET-Sensitive PPS states, respectively. These relative decreases were 7.02% for ET-resistant and 3.96% for ET-sensitive (49, 52).

10.3.3 HSUV results

The utilities shown in Table 41 were used in the model to calculate QALYs to reflect the improvements in HRQoL experienced by patients in the RIB + ET arm and the ET only arm. The applied utilities were age-adjusted to account for the decrease in HRQoL related to increasing age.

Table 41 Overview of health state utility values [and disutilities]

	No. Of patients	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs					
On-Treatment IDFS	[redacted]	[redacted]	EQ-5D-5L	DK	NA
Off-Treatment IDFS	[redacted]	[redacted]	EQ-5D-5L	DK	NA
NMR	[redacted]	[redacted]	EQ-5D-5L	DK	NA
DR	[redacted]	[redacted]	EQ-5D-5L	DK	NA
Disutilities					
Alanine aminotransferase increased	NA	-0.005	NICE TA 810	NA	NA
Neutropenia	NA	-0.007	NICE TA 810	NA	NA

10.4 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Not applicable.

10.4.1 Study design

Not applicable.

10.4.2 Data collection

Not applicable.

10.4.3 HRQoL Results

Not applicable.

10.4.4 HSUV and disutility results

Not applicable.

Table 42 Overview of health state utility values [and disutilities], N/A

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A				

Table 43 Overview of literature-based health state utility values, N/A

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A				

11. Resource use and associated costs

11.1 Medicine costs - intervention and comparator

The list of medicines, dosing and the pharmacy purchase Prices (PPP) is presented in Table 44. Ribociclib is available in three package sizes (21, 42 and 63 tablets) with a consistent tablet size of 200 mg regardless of package. The chosen 42 tablet package size is in line with the SmPC recommended posology in the adjuvant setting (400 mg).

Table 44 Medicine costs used in the model

Medicine	Dose	PPP, DKK	Relative dose intensity	Frequency	Vial sharing
Ribociclib	400 mg	15,537	83.40 %	21 days on 7 days off Max 3 years	NA
Letrozole	2.5 mg	34	99.03 %	QD	NA
Anastrozole	1 mg	38	99.03 %	QD	NA
Goserelin	3.6 mg	1,280	101.37 %	Implant every 3rd month	NA
Exemestane	25 mg	3,680	100 %	QD	NA
Tamoxifen	20 mg	150	100 %	QD	NA

The model does not consider medicine waste separately. Half-cycle correction is not applied to the TTD curve (as per DMC guidelines) and thus wastage stemming from unused last packages is included. Dosing of ribociclib in the eBC setting consist of 400 mg QD (200 mg x 2). As such, down dosing does not require the purchase of a new package, and no wastage is assumed due to down dosing. Consequently, using a relative dose intensity (RDI) of 1 would overestimate the cost of ribociclib. Since there is no wastage, the RDI from NATALEE of 333.58 mg has been used, which equates to 83.4%.

In the distant relapse states, an RDI of 1 has been used applied for palbociclib and abemaciclib to account for drug wastage. The choice is justified as these medicines do not have a similar single tablet dosing and have at list price level, flat pricing regardless of purchased package size. An RDI in line with clinical trials in the metastatic setting is applied to ribociclib for the same reasons as described in the adjuvant setting. For patients receiving RIB + ET, the model includes a TTD curve to estimate time on treatment with ribociclib and a separate TTD curve to estimate time on treatment with ET. This reflects a component of the trial design, whereby patients who discontinued ribociclib or placebo could continue receiving treatment with ET. Since the DCO of April 2024 occurred at the last treatment date of the last patient enrolled in NATALEE, the TTD of ribociclib was set equal to the KM of the TTD curve, as all patients in NATALEE had finished treatment. Both TTD curves are presented below in

Probabilities of TTD events for ET treatment for patients receiving ET in combination with ribociclib, and ET only were estimated using patient-level data from the NATALEE trial. As ET can be administered for a maximum of five years, the duration of the NATALEE trial follow-up was not sufficient to capture all treatment discontinuation activities related to the use of ET. For this reason, parametric distributions were fitted to patient-level data on TTD, which is presented in Appendix D.

Figure 11 selected TTD curves for ribociclib

Figure 12 selected TTD curves for ET in the ribociclib + ET and ET only arm

11.2 Medicine costs – co-administration

Ribociclib is indicated for the treatment of eBC in combination with an AI. In pre- or perimenopausal women, or in men, the AI should be combined with a LHRH agonist The recommended dose is 400 mg (two 200 mg film-coated tablets) of ribociclib once daily for 21 consecutive days followed by 7 days off treatment, resulting in a complete cycle of 28 days. Kisqali should be taken until completion of 3 years of treatment or until disease recurrence or unacceptable toxicity occur. When Kisqali is used in combination with an aromatase inhibitor (AI), the AI should be taken orally once daily continuously throughout

the 28-day cycle. The medicine costs of the co-administrations are included in the analysis and presented in Table 44 in the above section.

11.3 Administration costs

Administration costs are not included in the analysis. No costs are assumed for oral and subcutaneous administration as patients can administer subcutaneous injections at home without the help of a medical professional. Possible training for home injections is assumed to be captured in the disease management costs.

11.4 Disease management costs

Unit costs of healthcare services were based on the latest 'Honorartabel' for GP related costs and DRG 2025 rates for costs related to hospital visits. The frequency of resource utilization by health state were based on input from the clinical expert. Follow-up and monitoring costs were considered separately for the IDFS, NMR, DR, and Remission states. Specifics on the unit costs used to estimate the cost for services considered for follow-up and monitoring is available in Table 45 and Table 46.

Table 45 Disease management costs used in the model

Activity	Unit cost [DKK]	DRG code / description	Reference
GP visit	156.39	0202	Honorartabel
Mammogram	661	DRG 2025, 30PR14: Mammografi, ukompliceret	DRG 2025
Oncologist visit	1,578	09MA98: MDC09 1-dagsgruppe, pat. mindst 7 år	DRG 2025
ECG	287.37	0101 + 7156	Honorartabel
CT scan	2,701	30PR06, CT-scanning, kompliceret	DRG 2025
Mastectomy	154,495	09MP01: Mastektomi med rekonstruktion med stilket lap og dobbeltsidig mastektomi med protese	DRG 2025
Larger mammae operation	17,802	09MP05: Lille mammakirurgisk operation	DRG 2025
Lumpectomy	80,119	09MP02: Segmentresektion af bryst med onkoplastisk rekonstruktion og/el. kontralateral korrektion og enkeltsidig mastektomi med protese	DRG 2025
Radiotherapy	15,817	27MP13: Stråleplanlægning kompleks	DRG 2025
Patient time cost per visit	376	2 hour per contact	Værdisætning af enhedsomkostninger

Activity	Unit cost [DKK]	DRG code / description	Reference
Transportation cost	140.40	Average 40 km travel per visit used	Værdisætning af enhedsomkostninger
PET/CT	3,737	36PR37	DRG 2025
Chemotherapy	20,143	27MP21; Kemoterapi, kompleks	DRG 2025

The follow-up services included in the health economic model was based on clinical expert input. For several of the follow-up services these were assumed to incur at the same visit to not overestimate the costs of follow-up care, e.g. a patient visit was only counted once, when both a mammogram and an oncologists visit is counted and thus equates to the follow-up service with the highest visits, i.e. oncologists visits. A complete breakdown is presented in Table 46 below.

Table 46 Follow-up and monitoring services frequency and percent receiving by state

Service/Treatment	Health State	Frequency	Utilization Rate	Source
Follow-Up Services				
GP visit	Remission	Once a year starting in year two	100%	KOL input
Mammogram	iDFS	Once a year during first 4 years	100%	KOL input
	NMR	Every other year	100%	KOL input
	Remission	Once during first year	100%	KOL input
Oncologist Visit	IDFS	Two times in the first year, one time in year two and year three	100%	KOL input
	NMR	Once a year	100%	KOL input
	Remission	Once during first year	100%	KOL input
	DR	12 times per year	100%	KOL input
Patient time cost per visit	iDFS	Once a year	100%	KOL input
	NMR	Once a year	100%	KOL input
	Remission	Once a year	100%	KOL input
	DR	12 times per year	100%	KOL input
Transportation cost	iDFS	Once a year	100%	KOL input
	NMR	Once a year	100%	KOL input
	Remission	Once a year	100%	KOL input
	DR	12 times per year	100%	KOL input
CT scan	DR	Four time per year	100%	KOL input
Electrocardiogram	DR	Two times per year	70% ET-resistant 100% ET-sensitive	KOL input
Complete blood count	DR	12 times per year	100%	KOL input

Serum chemistry	DR	12 times per year	100%	KOL input
Mastectomy	iDFS	One-off	30.1%	KOL input
	NMR	One-off	59.4%	KOL input
Larger mammae operation	NMR	One-off	22.2%	KOL input
Lumpectomy	IDFS	One-off	69.9%	KOL input
	NMR	One-off	18.3%	KOL input
Radiotherapy	IDFS	One-off	90%	KOL input
	NMR	One-off	38.7%	KOL input
PET/CT	IDFS	One-off	100%	KOL input
	NMR	One-off	100%	KOL input

Additional treatment-specific healthcare resources for follow-up and monitoring were included for ribociclib (Table 47) and follows the same logic as described above.

Table 47 Additional treatment-specific follow-up and monitoring services in the iDFS state for the ribociclib + ET arm

Service Name	Description	Total Number of Services
Complete blood count	12 times during first year, and four times year two and year three	18
Liver function test	12 times during first year, and four times year two and year three	18
Electrocardiogram	Twice during first year	2
Oncologist visit	10 times during first year, and three times in year two and year three	16
Patient time cost per visit	12 times during first year, and three times in year two and year three	18
Transportation cost	12 times during first year, and three times in year two and year three	18

11.5 Costs associated with management of adverse events

The grade 3+ AEs with a difference of > 5% in either arm in the NATALEE trial that were considered treatment-requiring were included in the health economic model. Based on this, two AEs were included i.e., increased alanine amino transferase and neutropenia events. It was assumed that these two AEs can be managed with additional laboratory work and the costs of managing the AEs were thus based on the unit cost of an outpatient visit. The applied DRG 2025 tariffs are presented in Table 48. The cost of managing AEs was included as a one-off cost in the model.

Table 48 Cost associated with management of adverse events

Adverse event	DRG code	Unit cost/DRG tariff, DKK
Alanine amino transferase increased	DRG 2025, 23MA98: MDC23 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR740: Transaminase- og laktatdehydrogenaseforhøjelse	1,957
Neutropenia	DRG 2025, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD709: Neutropeni UNS	2,208

11.6 Subsequent treatment costs

Patients who progress from the iDFS health state to the DR health state, either directly or through the NMR health state, are assumed to enter either the ET-resistant or ET-sensitive health state. The proportion of patients on each subsequent therapy in both the ET-resistant and sensitive health states is presented in Table 49 and Table 50. The proportion receiving each regiment was based on input from the consulted clinical expert. The proportion of patients receiving each CDK 4/6 was based on the current tender and set to 85% for ribociclib, 12% for abemaciclib and 3% for palbociclib. All subsequent therapies described are administered orally and no additional costs are assumed for administration. An overview of all subsequent therapies, their dosing, cost, and RDI are presented in Table 51. The treatment length is assumed equal for all subsequent therapies, but vary by DR substate (ET resistant/ET sensitive) and arm (RIB + ET and ET only) and are presented in Table 52. Drug wastage is taken into consideration as described in section 11.1.

Table 49 Mix of subsequent treatments and RDIs in ET-resistant health state

Post-progression therapy (ET-resistant state)	RIB + ET	ET only	Relative dose intensity
Ribociclib + Fulvestrant	0.00 %	51.00 %	92.06 % ribociclib 100 % fulvestrant
Abemaciclib + Fulvestrant	0.00 %	7.20 %	100 % abemaciclib 100 % fulvestrant
Palbociclib + Fulvestrant	0.00 %	1.80 %	100 % palbociclib 100 % fulvestrant
Fulvestrant	30.00 %	20.00 %	100 %
Tamoxifen	10.00 %	10.00 %	100 %
Capecitabine	60.00 %	10.00 %	78 %

Table 50 Mix of subsequent treatments and RDIs in ET-sensitive health state

Post-progression therapy (ET-sensitive state)	RIB + ET	ET only	Relative dose intensity

Ribociclib + NSAI	51.00 %	59.50 %	87.5 % ribociclib 100 % letrozole
Abemaciclib + NSAI	7.20 %	8.40 %	100 % abemaciclib 50 % anastrozole 50 % letrozole
Palbociclib + NSAI	1.80 %	2.10 %	100 % palbociclib 100 % letrozole
Letrozole	20.00 %	15.00 %	100 %
Fulvestrant	10.00 %	15.00 %	100 %
Capecitabine	10.00 %	0.00 %	78 %

Table 51 Medicine costs of subsequent treatments

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity
Ribociclib	200	63	22,295.76	RIB + fulvestrant: 92.06 % RIB + NSAI: 87.50 %
Palbociclib	125	21	22,351.04	100 %
Abemaciclib	150	56	18,076.73	100 %
Fulvestrant	50	10	462	100 %
Everolimus	10	30	19,435	86 %
Exemestane	25	100	3,680	100 %
Letrozole	3	100	33.77	100 %
Anastrozole	1	100	38	100 %
Tamoxifen	20	100	150	100 %
Capecitabine	500	120	565.50	78 %

Table 52 Average treatment length for patients progressing from 1st line metastatic breast cancer treatment, i.e. PPS sub state in the DR health state.

DR sub-group	Treatment arm	Average duration of treatment (discounted)
ET sensitive	RIB + ET	[redacted]
	ET only	[redacted]
ET resistant	RIB + ET	[redacted]
	ET only	[redacted]

ET: Endocrine therapy; DR: Distant recurrence

Post-progression treatment costs in the distant recurrence states were estimated through input from the clinical expert, output from the health economic model and general costing. Firstly, we assumed that those who did not receive CDK 4/6 treatment in the 1st line metastatic setting would do so in the 2nd line and vice versa. Further, only 1st line of therapy in the PPS setting is included. Lastly, it was assumed there were no differences in cost between the ET resistant/sensitive patients after progression.

First, the proportion of patients who were ET resistant and ET sensitive were calculated from columns JK and JK in the comp1.Calc sheet. Then, the proportion of patients expected

to receive CDK 4/6 treatment in the 1st line DR treatment setting was calculated. This was done by using the above weightings and the inputted values for percent of patients receiving CDK4/6 in the ET resistant and ET sensitive treatment setting (Sheet: Treatment Mix & Dosing, cells: N185 and N201). Then, the expected cost of chemotherapy per cycle was calculated by dividing the DRG cost of chemotherapy (DRG 2025: 27MP21; Kemoterapi, kompleks; DKK 20143) with the average time spent in the PPS state. (Sheets: Comp1.Calc and Comp2.Calc, cell: PK695).

Lastly, the weighted cost of all the above was calculated, and the resulting post-progression treatment cost in the distant recurrence states was assumed to be 4,953.58 DKK per month. A more detailed calculation can be found in the health economic model on the "Cost & Resource use" sheet.

11.7 Patient costs

Patient time cost due to health care visits and transportation costs were included in the model. These are available in Table 53. The frequency of use and associated costs for these patient costs are presented in Table 46 and Table 47. The frequency was set as defined in section 11.4 and uses the standard costs set by the DMC with an assumption of 1 hour for transportation and 1 hour per visit on average, resulting in a cost of DKK 406 per patient time cost and DKK 140.40 per transportation cost.

Table 53 Patient costs used in the model

Activity	Time spent [minutes, hours, days]
Patient time cost per visit	2 hours per contact was assumed Værdisætning af enhedsomkostninger
Transportation cost	Værdisætning af enhedsomkostninger

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Palliative care cost was estimated at 89,879 DKK based on DRG 26MP47: Specialiseret Palliativ indsats, Øvrig. This cost was applied to all persons entering the dead state excluding those who enter the SPM absorbing state as death is not modeled for that population.

12. Results

12.1 Base case overview

The base case model overview is presented in Table 54.

Table 54 Base case overview

Feature	Description	
Comparator	Endocrine therapy	
Type of model	Semi-Markov Cohort Model with PSM modules	
Time horizon	40 years (lifetime)	
Treatment line	Adjuvant treatment	
Measurement and valuation of health effects	HRQoL measured with EQ-5D-5L in NATALEE. Danish population weights were used to estimate health-state utility values	
Costs included	Drug acquisition costs; 2) Medication administration costs and dispensing fees 3) Subsequent treatments costs (i.e., after recurrence) 4) Follow-up and monitoring costs 5) Adverse event (AE) costs; and 6) Terminal care costs.	
Dosage of medicine	Ribociclib 400mg plus ET (letrozole 2.5mg or anastrozole 1mg) and, for men and pre-menopausal women only, goserelin 3.6mg	
Average time on treatment (undiscounted)	[redacted]	
Parametric function for IDFS	RIB+ET: Gamma (I) ET: Gamma (I)	
Inclusion of waste	Not considered separately	
Average time in model health state (undiscounted)	RIB + ET [redacted]	ET only [redacted]

12.1.1 Base case results

Discounted deterministic base case results are presented in Table 55. The cost per QALY gained for ribociclib plus ET relative to ET only was estimated to be [redacted].

A summary of LYs, QALYs and costs by health state is also presented. Discounted LYs and QALYs were greatest for the iDFS health state. Gained LYs and QALYs were greatest for the iDFS state. It should be noted, that rounding in these results might offset the differences observed slightly.

Table 55 Base case results, discounted estimates

	RIB + ET	ET	Difference
Medicine costs	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]	[redacted]
Costs associated with management of adverse events	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]
Palliative care costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Life years gained (iDFS)	[redacted]	[redacted]	[redacted]
Life years gained (NMR)	[redacted]	[redacted]	[redacted]
Life years gained (Remission)	[redacted]	[redacted]	[redacted]
Life years gained (DR ET-resistant)	[redacted]	[redacted]	[redacted]
Life years gained (DR ET-sensitive)	[redacted]	[redacted]	[redacted]
Total life years	[redacted]	[redacted]	[redacted]
QALYs (IDFS)	[redacted]	[redacted]	[redacted]
QALYs (NMR)	[redacted]	[redacted]	[redacted]
QALYs (Remission)	[redacted]	[redacted]	[redacted]
QALYs (DR ET-resistant)	[redacted]	[redacted]	[redacted]
QALYs (DR ET-sensitive)	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental costs per life year gained		[redacted]	
Incremental cost per QALY gained (ICER)		[redacted]	

12.2 Sensitivity and scenario analyses

12.2.1 Deterministic sensitivity analyses

For the deterministic two-way sensitivity analysis, few scenarios were included and focus on those that were considered to have an impact on the results. The results of these are presented in the tornado diagram in Figure 13 below.

Figure 13 two-way sensitive analysis for select parameter changes.

ICER: Incremental cost effectiveness ration; ET: Endocrine therapy; NMR: non-metastic relapse

Several key parameters and model settings were changed to allow for a more nuanced view of the overall ICER. These different scenarios are presented in Table 56.

Table 56 Deterministic scenario analyses results

Scenario	Δ Costs	Δ QALYs	ICER
Base case	[redacted]	[redacted]	[redacted]
Short treatment effect waning (5-10 year)	[redacted]	[redacted]	[redacted]
No treatment effect waning	[redacted]	[redacted]	[redacted]
Time horizon of 10 years	[redacted]	[redacted]	[redacted]
Time horizon of 20 years	[redacted]	[redacted]	[redacted]
Alternate IDFS, Exponential	[redacted]	[redacted]	[redacted]
Alternate IDFS, Log-Logistic (R).	[redacted]	[redacted]	[redacted]
Alternate IDFS, Gamma (R).	[redacted]	[redacted]	[redacted]
Alternate IDFS, Weibull (R).	[redacted]	[redacted]	[redacted]
Add 25% tamoxifen to ET treatment basket (32)	[redacted]	[redacted]	[redacted]
Add 25% tamoxifen and 5% exemestane to ET treatment basket	[redacted]	[redacted]	[redacted]
Alternative IDFS, individual fitted curve, exponential, both, 8 to 16 year waning	[redacted]	[redacted]	[redacted]
Alternative IDFS, individual fitted curve, exponential, both, 8 to life-time waning	[redacted]	[redacted]	[redacted]
Alternative IDFS, individual fitted curve, log-logistic, both, 8 to 16 year waning	[redacted]	[redacted]	[redacted]
Alternative IDFS, individual fitted curve, log-logistic, both, 8 to life-time waning	[redacted]	[redacted]	[redacted]

Scenario	Δ Costs	Δ QALYs	ICER
Alternative IDFS, individual fitted curve, Gamma, both, 8 to life-time waning	[redacted]	[redacted]	[redacted]
Alternative IDFS, individual fitted curve, Weibull, both, 8 to 16 year waning	[redacted]	[redacted]	[redacted]
Alternative IDFS, individual fitted curve, Weibull, both, 8 to life-time waning	[redacted]	[redacted]	[redacted]
DBCG Data for type of event from IDFS	[redacted]	[redacted]	[redacted]
Same proportion of IDFS event for intervention and comparator	[redacted]	[redacted]	[redacted]

From the above table it is apparent that the time horizon has a major impact on the overall results, which is expected as treatment in the adjuvant setting is expected to incur its cost early during the first three years of treatment and the utility gain from reducing recurrences occurs on the time scale of decades. Further, treatment effect waning has a large impact on the results with longer waning periods leading to higher utility gain. The type of extrapolation has an influence, but the chosen curves do not have a major impact on the overall ICER. The type of event from the IDF state also has a major impact on the overall ICER. If Danish DBCG data is applied, this results in higher utility gain, however this result should be interpreted with caution, as it uses the type of IDFS event data from DBCG registry and time-to-event data from the NATALEE trial, with no type of adjustment. Lastly, adding TAM to the treatment basket also significantly effects the ICER, as tamoxifen has a lower efficacy vs. AI (HR: 0.66) (32, 98). TAM could be considered a valid comparator (see section 3.5), if the introduction of ribociclib in adjuvant setting changes the current treatment practice for ET, so that patients currently receiving TAM would instead receive an AI to become eligible for ribociclib. This is especially important, since this was the general opinion from the advisors at a recent Danish advisory board conducted by Novartis. [redacted]

12.2.2 Probabilistic sensitivity analyses

A probabilistic sensitivity analysis was carried out to give a representation of the robustness of the model. Appendix G shows all the parameters included, their distribution and the chosen variation. The average ICER in the PSA is [redacted]. Below in Table 57 and Figure 14 the results are presented. Overall, the scatter plot shows a long spread, which most likely is caused by the high variance of the mean age, which correlates well with the downward facing slope of the spread, since patients receiving treatment at a high age both incur lower QALYs but also do not reap the benefit over the long term. This large variation in the age of the population is most likely also the cause of the discrepancy between the deterministic base case and the results from the PSA. However, most of the highest cost patients who also benefit the least from treatment, will most likely not receive treatment in the adjuvant treatment setting, due to shared decision-making.

Table 57 Results from the probabilistic sensitivity analysis

	RIB + ET	ET	Difference
Costs (DKK)	[redacted]	[redacted]	[redacted]
Life Years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Incremental costs per life year gained		[redacted]	
Incremental cost per QALY gained (ICER)		[redacted]	

Figure 14 Scatter plot of the PSA, n=5000 simulations

[redacted]

13. Budget impact analysis

13.1 Patient population expected to be treated annually

As described in section 3.2, there are expected to be 537 patients treated with RIB + ET annually, if the full ITT population of NATALEE is reimbursed. Abemaciclib has been reimbursed in a subset of the NATALEE ITT population, and thus a proportion of patients are expected not to incur additional costs.

13.2 Budget impact if ribociclib is approved for treatment in the adjuvant setting

The budget impact has been simplified and only allocates the costs spent prior to recurrence. Since RIB + ET versus ET is superior, more costs are associated with treatment with RIB + ET prior to recurrence, and vice versa is true for ET only treatment and thus, this is considered a conservative choice.

We assume reimbursement is approved for ribociclib during the last quarter of 2025 with the implementation starting in January 2026. Therefore, no uptake in 2025 is expected. We expect to reach the peak of treated patients by year 3, with 50% and 75% treatment volume in year 1 and year 2 respectively. Lastly, we assume that 50% of patients diagnosed

with HR+/HER2-eBC one year prior to the approval date of ribociclib by the DMC will be recalled to the clinic and treated, when implementation starts.

The patient assumptions are the same as presented in section 3.2, however for the population shared with abemaciclib the assumptions differ (41% of NATALEE eligible patients as per DBCG registry). From the DBCG data, 380 patients would be eligible in the shared population for treatment with abemaciclib/ribociclib. Of these 93.4% are expected to be treated with ET and 85% percent are assumed to receive the recommended treatment through shared decision-making (The percentage of patients receiving CDK4/6 is assumed to be higher in the overlapping population). With these assumptions, 302 patients are expected to receive abemaciclib. The overlapping population does not include those treated with TAM and as per section 3.2 these are assumed to account for 25%, leaving 266 patients in the shared population. With these assumptions, the below patients estimated to be treated with ribociclib + ET in the adjuvant treatment setting of HR+/HER2- early breast cancer is 311 new patients annually, with a budget impact of approximately 130 million in year 5, using list prices. Below, in Table 58 and Table 59, the results are presented.

Table 58 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
Recommendation					
RIB + ET	310	233	310	310	310
ET only	155	77	0	0	0
Non-recommendation					
RIB + ET	0	0	0	0	0
ET only	465	310	310	310	310

Table 59 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The medicine under consideration is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

14. List of experts

Ann Søegaard Knop, Region H, chief physician, and head of DBCG's medical committee, has been consulted as a clinical expert to validate assumptions in the clinical dossier (i.e. patients estimate, comparators, endpoint validation, current treatment pathway etc.), and for input data for the health economic model.

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Appendix A. Main characteristics of studies included

Table 60 Main characteristics of NATALEE

Trial name: NATALEE (5)	NCT number: NCT03701334
Objective	The purpose of the NATALEE trial was to evaluate efficacy and safety of ribociclib with endocrine therapy as adjuvant treatment in patients with HR+/HER2- Early Breast Cancer (5).
Publications – title, author, journal, year	Second-interim analysis: Slamon et al. 2024. Ribociclib plus Endocrine Therapy in Early Breast Cancer. N Engl J Med. 2024 Mar 390(12), 1080–1091. DOI: 10.1056/NEJMoa2305488. PMID: 38507751 (5). Second-interim, PRO data: Novartis Pharmaceuticals. A phase III, multicenter, randomized, open-label trial to evaluate efficacy and safety of ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, HER2-negative, early breast cancer: efficacy analysis and safety update (11-Jan-2023 data cut-off). (Data on file) 2023. (51) Final iDFS analysis: Hortobagyi G, Stroyakovsky D, Yardley D*, et al.* Ribociclib (RIB) plus nonsteroidal aromatase inhibitor (NSAI) as adjuvant treatment in patients with HR+/HER2-early breast cancer: final invasive disease-free survival (iDFS) analysis from the NATALEE trial. Cancer Research. 2024;84(9). (6) 4-year landmark analysis (no peer-review publications yet): Fasching PA. LBA13 Adjuvant ribociclib (RIB) plus nonsteroidal aromatase inhibitor (NSAI) in patients (Pts) with HR+/HER2− early breast cancer (EBC): 4-year outcomes from the NATALEE trial. Ann Oncol. 2024;35:S1207.(7) Peter A. Fasching DS, Denise A. Yardley, Chiun-Sheng Huang, John Crown, Aditya Bardia, Stephen Chia, Seock-Ah Im, Miguel Martin, BingheXu, Sherene Loi, Carlos Barrios, Michael Untch, Rebecca Moroose, Frances Visco, Gabriel N. Hortobagyi, Dennis J. Slamon, YaninaOviedo, Sorcha Waters, Sara A. Hurvitz. Adjuvant Ribociclib Plus Nonsteroidal Aromatase Inhibitor in Patients With HR+/HER2− Early Breast Cancer: 4-Year Outcomes From the NATALEE Trial. LBA13. Oral Proffered Paper. ESMO2024. (8) Novartis Pharmaceuticals. A phase III, multicenter, randomized, open-label trial to evaluate efficacy and safety of ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor positive, HER2-negative, early breast cancer: End of Ribociclib Analysis Report (4-year landmark). (Data on file) 2024.(9)

Trial name: NATALEE (5)	NCT number: NCT03701334

Study type and design	The NATALEE trial was a phase 3, multi-center, randomized, open-label study involving patients with HR-positive, HER2-negative early breast cancer. Patients were randomly assigned in a 1:1 ratio to receive either ribociclib 400 mg once daily on days 1-21 of a 28-day cycle and endocrine therapy once daily continuously or ET only once daily continuously (5).
Sample size (n)	5,101 patients were randomly assigned to receive either ribociclib plus an NSAI (2,549 patients) or an NSAI alone (2,552 patients). As of the 3-year data cut-off (January 11, 2023) 1,984 patients (77.8%) in the ribociclib–NSAI group were either still receiving ribociclib plus an NSAI or were continuing to receive an NSAI, and 1,826 (71.6%) in the NSAI group were still receiving an NSAI. Overall, 515 patients (20.2%) completed the planned 3 years of treatment with ribociclib. At the 4-year data cut-off (April 29, 2024), 1601 patients corresponding to 62.4% had completed the 3-year treatment and all patients were off ribociclib (9).
Main inclusion criteria (5)	• Men or pre- or postmenopausal women aged ≥18 years • Histologically confirmed unilateral primary invasive adenocarcinoma of the breast with a date of initial cytologic or histologic diagnosis within 18 months prior to randomization • Anatomic stage group II or III disease • BC that is positive for ER and/or PR, and negative for HER2 • Complete surgical resection, with the final surgical specimen microscopic margins free from tumor • Completion of (neo)adjuvant chemotherapy (if indicated) and adjuvant radiotherapy (if indicated) • Permitted to have already received any standard (neo)adjuvant ET but must be randomized within 12 months of the initial start date of the ET • ECOG performance status of 0 or 1 • Adequate bone marrow and organ function • Standard 12-lead ECG values assessed by a central laboratory as follows: • QTcF interval (QT interval using Fridericia's correction) at screening < 450 msec • Resting heart rate 50–90 beats per minute (determined from the ECG)
Main exclusion criteria (5)	• Prior treatment with a CDK4/6 inhibitor • Prior treatment with TAM, raloxifene, or AI for reduction in risk of BC and/or prior treatment for osteoporosis in the preceding 2 years

Trial name: NATALEE (5)	NCT number: NCT03701334
	• Prior treatment with anthracyclines at cumulative doses of 450 mg/m² or more for doxorubicin or 900 mg/m² or more for epirubicin • Hypersensitivity to any of the excipients of ribociclib and/or ET • Distant metastases of BC beyond regional lymph nodes and/or evidence of recurrence after curative surgery • Concurrent usage of other antineoplastic therapy with the exception of adjuvant ET • Patient has not recovered from clinical and laboratory acute toxicities related to prior anticancer therapies (NCI CTCAE version 4.03 grade ≤1) at the day of randomization • Concurrent invasive malignancy or a prior invasive malignancy whose treatment was completed within 2 years before randomization • Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormalities • Currently receiving strong CYP3A4/5 inhibitors or inducers, or medications that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5 • Currently receiving or has received systemic corticosteroids ≤2 weeks prior to starting the study treatment or has not fully recovered from side effects
Intervention	The ribociclib–NSAI group received ribociclib (400 mg, administered orally once daily for 21 consecutive days, followed by 7 days off, for a complete cycle of 28 days, administered for 36 months) plus a nonsteroidal aromatase inhibitor (NSAI; letrozole 2.5 mg, administered orally once daily, or anastrozole 1 mg, administered orally once daily, on a continuous schedule for 60 months). Patients in the ribociclib–NSAI group were expected to continue to receive the NSAI after completing the 36 months of treatment with ribociclib and were considered to be receiving trial treatment during this time. Additional treatment with the NSAI beyond 60 months was at the discretion of the treating physician and was not considered to be part of the trial treatment. Men and premenopausal women in both groups also received goserelin for gonadal suppression (3.6 mg, administered subcutaneously once every 28 days).
Comparator(s)	The NSAI group received ET only with letrozole at a dose of 2.5 mg per day or anastrozole at a dose of 1 mg per day for ≥5 years.
Follow-up time	As of the 3-year data cut-off the median duration of follow-up (from randomization to the data cut-off on January 11, 2023) for primary efficacy endpoints was 27.7 months. The median duration of exposure to the study treatment was 30.1 months in the ribociclib-NSAI group

Trial name: NATALEE (5)	NCT number: NCT03701334
	and 30.0 months in the NSAI group. Only PRO-data rely on this data-cut. (51) At the 4-year data cut-off, the median duration of follow-up (from randomization to the data cut-off on April 29, 2024) for primary efficacy endpoints was 44.2 months. The median duration of exposure to the trial treatment was 45.1 months in the ribociclib–NSAI group and 45.0 months in the NSAI group (9).
Is the study used in the health economic model?	Yes.

Primary, secondary and exploratory endpoints (99)	**Primary efficacy endpoint**
	• iDFS
	  ○ Defined according to STEEP criteria, version 1.0, as assessed by the investigator.
	  ○ iDFS is defined as time from the date of randomization to the date of the first event of local invasive breast recurrence, regional invasive recurrence, distant recurrence, death (any cause), contralateral invasive BC, or second primary non-breast invasive cancer (excluding basal and squamous cell carcinomas of the skin).
	
	Secondary efficacy endpoints
	• RFS
	  ○ RFS using STEEP criteria.
	  ○ RFS is defined as the time from date of randomization to date of first event of local invasive breast recurrence, regional invasive recurrence, distant recurrence, or death (any cause).
	• DDFS
	  ○ DDFS using STEEP criteria.
	  ○ DDFS is defined as the time from date of randomization to date of first event of distant recurrence, death (any cause), or second primary non-breast invasive cancer (excluding basal and squamous cell carcinomas of the skin).
	• OS
	  ○ Defined as the time from date of randomization to date of death due to any cause.
	
	Safety endpoints
	• Frequency and severity of adverse event
	• laboratory and Electrocardiogram (ECG) abnormalities
	
	PRO and HRQoL endpoints
	• EORTC core quality of life questionnaire (EORTC QLQ-C30, version 3.0)
	• EORTC BC specific quality of life questionnaire (EORTC QLQ-BR23, version 1.0)

Trial name: NATALEE (5)	NCT number: NCT03701334
	• Generic health utility measure EuroQoL 5-level instrument (EQ-5D-5L) • Hospital Anxiety and Depression Scale (HADS) questionnaire **Other endpoints** • Pharmacokinetics of ribociclib ○ Geometric mean trough plasma concentration of ribociclib **Exploratory endpoints** • LRRFS defined as time from date of randomization to date of first event of local invasive breast recurrence, regional invasive recurrence, or death due to any cause **Endpoints included in this application:** • iDFS • DDFS • OS • Change from baseline in the physical functioning sub-scale score as assessed by EORTC QLQ-C30 • Change from baseline in VAS EQ-5D
Method of analysis	The efficacy analyses were performed in the intention-to-treat population, which included all the patients who had undergone randomization. The safety analyses were performed in the safety population, which included all the patients who had undergone randomization and had received at least one dose of the trial treatment. Invasive disease–free survival (the primary end point) was compared between the groups with the use of a stratified log-rank test; the same stratification factors that were used for randomization were applied to the analysis. We estimated that 500 events (invasive disease, recurrence, or death) would need to occur to provide the trial with approximately 85% power to detect a hazard ratio for invasive disease, recurrence, or death of 0.76 at a one-sided alpha level of 0.025. This report is based on all data collected up to the time of the protocol-specified second interim efficacy analysis (January 11, 2023), which was performed after 426 events had occurred. At the time of this analysis, a prespecified Lan–DeMets (O'Brien–Fleming) stopping boundary of a one-sided P-value threshold of 0.0128 was used by the independent data monitoring committee to conclude that treatment with ribociclib plus an NSAI was significantly superior to an NSAI alone with respect to efficacy; the two-sided stopping boundary (P-value threshold, 0.0256) is reported. All time-to-event end points were evaluated with the use of the Kaplan–Meier method. Hazard ratios were estimated by means of a stratified Cox proportional-hazards model. All reported 95% confidence intervals are two-sided. The widths of the confidence intervals have not been adjusted for multiplicity and thus may not be used in place of

Trial name: NATALEE (5)	NCT number: NCT03701334
	hypothesis testing. The secondary end points were compared between the groups with the use of a stratified log-rank test.
Subgroup analyses	Subgroup analyses were performed as pre-specified subgroups by menopausal status, AJCC stage (American Joint Committee on Cancer), prior chemotherapy, prior ET, region, historical grade at time of surgery, Ki-67 status from archival tumor tissue, and nodal status according to AJCC staging (5).
Other relevant information	None.

Appendix B. Efficacy results per study

Results per study

Table 61 presents an overview of the results per the NATALEE study and the methods used to generate the results.

Table 61 Results per study

Results of NATALEE (NCT03701334)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
iDFS rate (4-year)	RIB + ET	2,549	88.5% (87.1–89.8)	4.9%	Not reported	Not reported	HR: 0.715	0.609–0.840	<0.0001	Hazard rate in ET + ribociclib versus hazard rate in ET only is from 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 ET only group is the reference in the hazard ratio calculation. One-sided P-value	Novartis 4-Year landmark analysis (data on file (9), presented by Fasching at ESMO 2024 (8)
	ET only	2,552	83.6% (81.8–85.2)								

Results of NATALEE (NCT03701334)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*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).	
DDFS rate (4-year)	RIB + ET	2,549	89.4% (88.0–90.7)	4.5%	Not reported	Not reported	HR: 0.715	0.604–0.847	<0.0001	See above	Novartis 4-Year landmark analysis (data on file)
	ET only	2,552	84.9% (83.2–86.5)								
DRFS rate (4-year)	RIB + ET	2,549	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	See above	Novartis 4-Year landmark analysis (data on file)
	ET only	2,552	[redacted]								
OS rate (4-year)	RIB + ET	2,549	95.0% (94.0–95.9)	0.8%	Not reported	Not reported	HR: 0.827	0.636–1.074	0.0766	See above	Novartis 4-Year landmark

Results of NATALEE (NCT03701334)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	ET only	2,552	94.2% (93.0–95.2)								analysis (data on file)

Appendix C. Comparative analysis of efficacy

The comparison of RIB + ET vs. ET only was a head-to-head comparison based on the NATALEE RCT. Thus, the results from the comparative analysis are presented in Appendix B.

Table 62 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication], NA

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
NA									

Appendix D. Extrapolation

Extrapolation of IDFS

D.1.1 Data input

Probabilities of IDFS events for patients receiving RIB + ET and ET only were based on the April 29, 2024, data cutoff of NATALEE. Parametric distributions fit to patient-level data on IDFS were evaluated based on the criteria described in section 8.1

The IDFS curve from the NATALEE trial has been used as the main source of efficacy data in the health economic model. Survival distributions were estimated to the IDFS curve and patients were distributed to health states according to type of event as described in section 4.2.

D.1.2 Model

Parametric survival distributions were fitted to failure time data from NATALEE using FlexSurv, an R package for fully-parametric modelling of survival data (100). The following parametric distributions were estimated:

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

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

The distributions used in the model were selected based on fit statistics, visual inspection of survival distributions, hazard functions, time dependent hazard ratios, and diagnostic plots for treatment effects, as well as clinical plausibility. The Bayesian Information Criteria (BIC) was used as the primary measure of statistical fit, as this statistic places a relatively high penalty on the number of parameters included in the distribution and hence avoids placing undue influence on the tail of the distribution which can have a large effect on long term survival projections.

Plots of Schoenfeld residuals were generated to assess the proportional hazards assumption. Schoenfeld residuals are calculated at each failure time by taking the difference of the covariate value for the patient and a weighted average covariate value of patients remaining in the risk set at that time. The scaled residuals are then obtained

by multiplying the vector of unscaled residuals by the inverse of their covariance matrix. The scaled residuals can then be used as a time-dependent measure of the treatment effect. An increasing or decreasing trend in the Schoenfeld residuals can be used to detect a deviation from proportional hazards. Because the treatment group covariate is a binary variable, the scaled residuals will either appear well above or below the mean, depending on the group in which the failure occurred. To make the pattern of these residuals easier to visualize, a kernel-smoothed estimate will be provided. To test proportionality of hazards, the slope of the scaled Schoenfeld residuals was tested using linear regression.

Survival distributions for IDFS and TTD for the two treatment groups were estimated using three alternative approaches for parameterizing the effect of treatment on IDFS times:

- "Restricted" models in which a single parameter of the survival distribution is allowed to differ between groups.
- "Unrestricted" models in which all parameters of the survival distribution are allowed to differ between groups.
- Individual models in which all parameters of the survival distribution are allowed to differ between groups.

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

For example, a Weibull distribution has two parameters: a scale parameter and shape parameter. With the restricted Weibull distribution, the scale parameter is permitted to differ between arms, but the shape parameter is assumed to be the same. With an unrestricted Weibull distribution, both the shape and the scale parameters are permitted to differ between arms. The restricted Weibull is a proportional hazard model whereas the unrestricted Weibull is not. The use of this approach for parameterizing treatment effects permits the comparison of models in which the effect of treatment is and is not interacted on different distributional parameters using conventional fit statistics such as the BIC.

In the individual models, there are no treatment effect assumptions between the two curves and thus, they are completely independent. These parameterization curves were not part of the global model delivery and have been made especially for inclusion in this submission. It should be noted that parameter estimates from individually fitted curves may be akin to unrestricted parametric estimates since a) Unrestricted models have more relaxed assumptions, with all parameters allowed to vary between arms. This may lead to similarity in estimates to individually fitted models/curves and b) For unrestricted models,

a mathematical link remains between the two arms in the form of treatment effects, but the parameter estimates for each arm may still end up close to individually fitted curves.

Conceptually and mathematically, unrestricted and individual models are different and within this context, we believe that unrestricted curves are not a fit per the DMC guidelines and they are not explored further in this submission. However, we have kept these in the cost-effectiveness model for completeness. Below in Table 63, an overview of the differences between the three models are presented.

Table 63 Differences between restricted, unrestricted and individual parametric curve fitting

Restricted model	Unrestricted model	Individual fitting
Assumes that a single parameter varies between arms, other parameters remain same A treatment effect is estimated based on this parameter (e.g., a shape parameter) Estimated from same statistical model for both arms	Assumes all parameters vary between arms, and treatment effect is estimated Treatment effect may be estimated for all the parameters, E.g., Shape (Treatment) = Shape(placebo) X exp(treatment effect shape) Scale (Treatment) = scale(placebo) X exp(treatment effect scale) Estimated from same statistical model for both arms, but with relaxed assumptions on parameters compared to restricted models	Distributions/curves are fitted individually to each arm, no concept of a treatment effect parameter exists. Parameters estimated independently for each treatment arm.

D.1.3 Proportional hazards

KM survival and hazard rates by treatment group, the HR for RIB + ET versus ET only, and RMST by treatment group for all patients in the NATALEE trial are reported in Figure 15. Hazard rates for the RIB + ET arm appear to peak relatively early, approximately after 6 months, with a slow steady decline over the remaining follow-up. Hazard rates for the ET only arm is initially stable and then increase, reaching a peak after month 42. The plot of time-dependent hazard ratios demonstrates a great degree of oscillation between being below and above one.

Figure 15 Invasive Disease-Free Survival for the ITT Population in NATALEE, by Randomized Treatment

A. Kaplan-Meier Surival Distribution

B. Hazard rates

C. Hazard ratio

D. Restricted Mean Survival Time

Transformation and treatment effect diagnostic plots for iDFS of the ITT population of NATALEE are shown in Figure 15. The plots of the –ln(survival) vs. months, representing the cumulative hazard function, are straight lines for the most part, suggesting relatively constant hazards. The cumulative hazards do increase at the tail of the distribution, consistent with an increase in hazard at that time, although the numbers at risk are small and thus any interpretation of the tail should be made with caution. The plot of ln(time) over ln(-ln(survival) curves crosses near the beginning of follow-up but are otherwise straight and parallel. These things combined could indicate a violation of the proportional hazard assumption.

Figure 16 Transformation and Treatment Effect Diagnostic Plots for Invasive Disease-Free Survival of the ITT Population in NATALEE, by Randomized Treatment

A. Transformation Diagnostics

B. Treatment Effect Overlay Diagnostic Plots

ET: Endocrine therapy

A plot of a smoothed curve fit to Schoenfeld residuals for IDFS of the ITT population of NATALEE is shown in Figure 17. The curve is virtually a straight line and the p-value on the test of non-proportionality (0.538) is not significant suggesting that the PH assumption is not unreasonable.

Figure 17 Plot of Smoothed Curve Fit to Schoenfeld Residuals for IDFS of the ITT Population in NATALEE

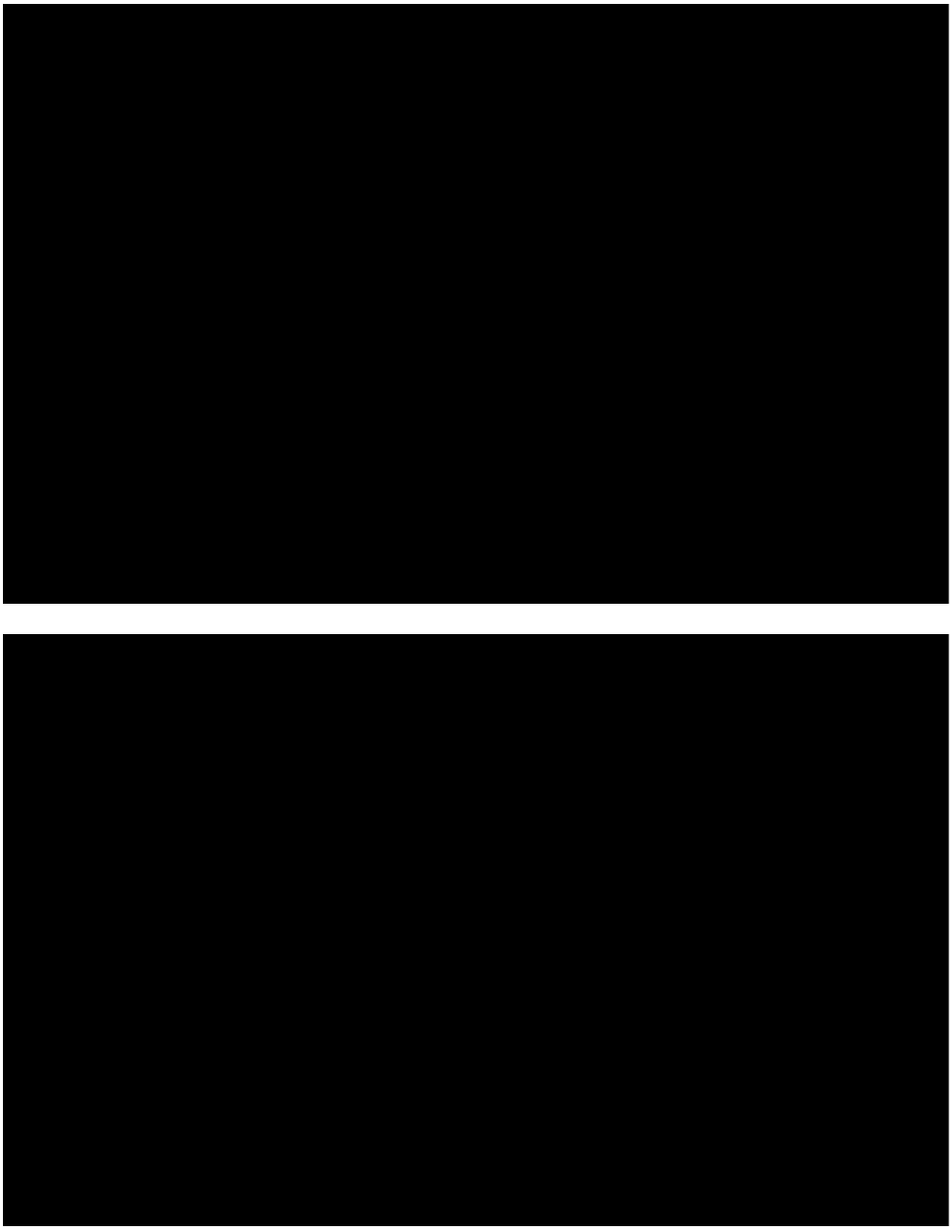
iDFS: invasive disease-free survival; HR: Hazards ration; ITT: intention to treat

D.1.4 Evaluation of hazard functions

A smoothed Hazard plot was overlayed on the projected hazards curves. From the figure, it is difficult to tell which parametric functions fits the data best. Moreover, near the end of follow-up, when the tail is prone to confounding due to the small sample size, there is a spike in the RIB + ET arm. Analyzing the unsmoothed data shown in Figure 19, it is apparent that the steep curve of the smoothed hazards plot near the end is due to the steep incline when only few people remain in the trial. As such this is most likely an overcorrection, as the hazards appear to remain unchanged until month 50, where 312 and 282 patients remain at risk for the RIB + ET and ET arms, respectively (data on file).

From the graphs shown, it is possible to determine that some parametric functions do not fit the data well in the beginning of the trial. The exponential function does not fit the data for both arms, the Gompertz function does not fit the RIB + ET arm and the log-normal function does not fit the ET only arm.

Figure 18 RIB + ET and ET only Parametric Hazard Rates to End of Trial Follow-up



ET: Endocrine therapy

Figure 19 Hazard Rates, using Pehaz (interval) and Muhaz (smoothed) functions

ET: Endocrine therapy

D.1.5 Evaluation of statistical fit (AIC and BIC)

Discussed collectively in section D.1.8

D.1.6 Evaluation of visual fit

Discussed collectively in section D.1.8

D.1.7 Validation and discussion of extrapolated curves

Discussed collectively in section D.1.8

D.1.8 Parametric fitting of the RIB + ET arm

D.1.8.1 Restricted and unrestricted model

A ranking of parametric distributions fit to IDFS by the fit statistics are shown in Table 64. The best fitting distributions based on the Akaike's Information Criterion (AIC) AIC and corrected AIC (AICc) are consistent with those based on the BIC for the top 3 best fitting distributions and then diverge. The exponential distribution had the best statistical fit based on the BIC, though the range of BICs among the top six best-fitting distributions was 11 (8157 for exponential to 8168 for Gompertz restricted). It is not surprising that the exponential distribution is ranked higher with BIC than with AIC and AICc as the BIC metric places a higher penalty on the number of parameters than the latter; the exponential distribution has only one parameter.

Table 64 Fit Statistics for Parametric Distributions fit to IDFS of the ITT Population in NATALEE

Distribution	AIC	AICc	BIC
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

AIC: Aikaike information criterion; AICc: Aikaike information criterion corrected; BIC: Bayesian Information criterion; R: Restricted; U: Unrestricted

Parametric survival distributions for IDFS during the trial period for the best fitting distributions based on BIC are shown in Figure 20. The visual fit of the parametric distributions to the KM curves are all reasonably good and very similar in fit. All the fitted distributions are within the 95% CIs for the KM distributions throughout the trial follow-up to the point where it is difficult to say that one distribution has better visual fit compared with the others.

Figure 20 Parametric Survival Distributions Fit to IDFS of the ITT Population in NATALEE, by Randomized Treatment

Best fitting distributions based on BIC are shown. Distributions are ranks by BIC (left to right, top to bottom). R: restricted; iDFS: invasive disease-free survival; ET: Endocrine therapy; ITT: intention to treat

Long-term projections of IDFS (out to 20 years) for these distributions are shown in Figure 21. Five of the best fitting parametric distributions according to BIC, exponential, log-logistic restricted, gamma restricted, Weibull restricted, and RCS Weibull restricted yield very similar long-term projections, with projected IDFS for ribociclib at approximately 50% by 20 years and 35% to 40% for ET. The restricted Gompertz distribution yields much lower long-term survival projections than the other top fitting distributions, with survival at 20 years approximately 10% lower for either arm compared with the other distributions shown. It should be noted that these projections do not incorporate non-eBC mortality, which is captured separately in the model.

Figure 21 Long-Term Projections of IDFS Based on Parametric Survival Distributions fit to IDFS for the ITT Population in NATALEE, by Randomized Treatment

Best fitting distributions based on BIC are shown. Distributions are ranks by BIC (left to right, top to bottom).
ET: Endocrine therapy; iDFS: invasive disease-free survival; R: restricted; ITT: intention to treat

Figure 22 Long-Term Projections of IDFS Based on Parametric Survival Distributions fit to IDFS for the ITT Population in NATALEE, by Randomized Treatment in the same figure.

RMST to 60 months (i.e., end of trial follow-up) and 20 years is shown in Table 65. Projected RMST for IDFS with ribociclib after 20 years ranges from [redacted]. The difference in RMST for ribociclib vs. ET only, which approximates the long-term IDFS benefit that would be generated by the economic model, ranges from [redacted]

([redacted]). The estimated difference in RMST for the two best fitting distributions, the exponential and gamma restricted, [redacted], respectively. It should be noted that the RMST estimates below are not adjusted for background mortality or treatment effect waning assumptions.

Table 65 RMST in months for IDFS to End of Trial Follow-up and 20 Years among the Full Population of NATALEE, by Randomized Treatment Arm

Distribution	End of Trial Follow-Up			20 Years		
	RIB + ET	ET only	Difference	RIB + ET	ET	Difference
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

iDFS: invasive disease-free survival; R: restricted; U: Unrestricted; RMST: Restricted mean survival time

Figure 23 Long term extrapolation overlayed Kaplan-Meier data for the four best fitting restricted curves for RIB + ET and ET only

iDFS: invasive disease-free survival; ET: Endocrine therapy; ITT: intention to treat; R: restricted

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 a subjective assessment of the clinical plausibility of long-term extrapolations. Gamma (R), Weibull (R) and log-logistic (R) all have almost identical statistical fit but yields large long-term differences. [redacted]. To this, any treatment effect waning is not applied and thus the difference would be smaller after this application.

The gamma restricted distribution ranked third in goodness of fit based on BIC and had excellent visual fit to the K-M IDFS for both arms in NATALEE. [redacted]. While a lower BIC value indicates better statistical fit, the BICs for these two models are so similar as to almost be indistinguishable on this metric. Furthermore, the gamma restricted distribution had estimated difference in [redacted], which was also the median of differences in projected RMST across all fitted models. The difference in RMST approximates the projected benefit in IDFS for RIB + ET vs. ET only. Results from all four best fitting restricted parameterization curves have been explored in scenario analyses.

Individually fitted parametric curve for RIB + ET

The unrestricted and restricted parametric models are jointly fitted and thus require there to be a connection between the two arms. From the section above, we argue that the proportional hazards assumptions are not unreasonable. However, in our base case we have chosen to use individually fitted curves, which are detailed in the section below.

Choice of parametric fit is, as with the jointly fitted curves, extensively explored in scenario analyses.

RIB + ET arm

All parametric functions seem to visually fit the data well within the trial period (Figure 24), but many of these diverge greatly after end of follow-up and will produce too optimistic or too pessimistic outcomes if chosen, as can be seen from Figure 25.

Figure 24 RIB + ET IDFS individual curve fittings, 7 years

ET: Endocrine therapy; iDFS: invasive disease-free survival; I: individual

Figure 25 Ribociclib plus + ET IDFS individual curve fittings, 50 years

The statistically best fitting curves are the exponential, gamma, Gompertz, log-logistic, lognormal, Weibull, RCS Weibull, and RCS log-logistic as can be seen in the table below. Both the Lognormal and the Gompertz produce too optimistic and pessimistic results and are therefore not explored further. Although the RCS Weibull and RCS log-logistic curves show an excellent fit in terms of AIC statistics, they have not been explored further, since the hazards seem to remain relatively constant as depicted in Figure 15 and Figure 19.

Table 66 AIC/BIC statistics for individual fitted curves for the RIB + ET arm

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Gen. Gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]
Gen F	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
RCS Weibull	[redacted]	[redacted]
RCS Log-Logistic	[redacted]	[redacted]

ET: Endocrine therapy; AIC: Akaike information criterion; BIC: Bayesian information criterion; Gen: Generalized; RCS: restricted cubic spline

Figure 26 Lifetime projection of the four best fitting curves

ET: Endocrine therapy; iDFS: invasive disease-free survival; I: Individual; K-M: Kaplan Meier

From Figure 26, the Weibull and the gamma functions produce the most pessimistic survival curves, whereas the log-logistic produce the most optimistic curves.

The exponential curve has the best statistical fit in terms of BIC. However, this metric penalizes parametric functions on their complexity and thus the exponential would be expected to have a lower value. The log-logistic curve follows the exponential curve up till year 17 where they start to diverge and the log-logistic produces more optimistic long-term survival. Note, that choosing between these two would have little effect on the outcome of the health economic model, as treatment effect waning is applied starting at year 8.

ET only arm

The individually fitted curves for the ET only arm shows a good fit within the trial periods, besides the exponential and the lognormal curve (Figure 27). As with the iDFS curve fittings of RIB + ET, many of these diverge greatly after end of follow-up and will produce too optimistic or too pessimistic outcomes if chosen (Figure 28).

Figure 27 7-year projection of the individually fitted parametric curves to the ET only arm

ET: Endocrine therapy; ITT: intention to treat; iDFS: Invasive disease-free survival; I: Individual; K-M: Kaplan Meier

Figure 28 50-year projection of the individually fitted parametric curves to the ET only arm

ET: Endocrine therapy; ITT: intention to treat; iDFS: Invasive disease-free survival; I: Individual; K-M: Kaplan Meier

From Figure 18 and Figure 19, some changes in the smoothed hazard can be observed. However, the RCS curves fit the data poorly statistically and have thus not been explored further. The inclusion of these is attenuated by the fact they follow their regular fittings closely.

The statistically best fitting curves are exponential, gamma, Gompertz, log-logistic and Weibull. However, the Gompertz extrapolation seem to produce unrealistic results and are therefore not considered further.

Table 67 AIC/BIC statistics for individual fitted curves to the ET only arm

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Gen. Gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]
Gen F	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
RCS Weibull	[redacted]	[redacted]
RCS Log-Logistic	[redacted]	[redacted]

ET: Endocrine therapy; AIC: Akaike information criterion; BIC: Bayesian information criterion; Gen: Generalized; RCS: restricted cubic spline

Figure 29 50-year projection of the four best fitting individual curves for the ET only arm

ET: Endocrine therapy; ITT: intention to treat; iDFS: Invasive disease-free survival; I: Individual; K-M: Kaplan Meier

The four best statistical fitting curves show similar survival times, and all follow the trial data well, but start to disperse around year five. The gamma and Weibull curves are the more conservative estimates, with log-logistic being high and exponential falling in between, though this dispersion only starts after year 12.

No data exists on NATALEE eligible patients, making long-term survival projections difficult, and arguing whether the more optimistic case is correct versus the more pessimistic is futile. However, it is noted that the log-logistic curve produces an optimistic case, whereas the gamma and Weibull are on the pessimistic side, with the exponential function falling in between. The exponential being a good fit to the trial data contrasts with the poor fit of the exponential function to the smoothed hazard function and the fact that it does not follow the data well within the trial period. However, the effect on the short-term survival estimates is minor compared to the long terms effects on the overall results.

Figure 30 Graph showing the four best fitting parametric curves between the RIB + ET arm and the ET only arm

ET: Endocrine therapy; ITT: intention to treat; iDFS: Invasive disease-free survival; I: Individual; K-M: Kaplan Meier

Since no evidence exist that could inform a choice between two different parametric functions for long-term extrapolation, we have chosen to use the same extrapolation function in both arms. We have chosen the gamma-functions for the same reasons as listed under the section regarding restricted parametric fitting, with it producing results close to the median estimated RMST.

D.1.9 Adjustment of background mortality

Probabilities of transitioning to the Death state were adjusted for general population mortality, with sex- and age-specific lifetables applied as a floor.

D.1.10 Adjustment for treatment switching/cross-over

N/A, as no switching/cross-over allowed

D.1.11 Waning effect

When assessing medicinal products, the uncertainty of the long-term effects is sometimes conservatively adjusted, by implementing treatment effect waning, in which the effect of the intervention arm is lowered or made equal to the comparator arm over time.

For this STA, treatment effect waning was implemented such that the hazard of recurrence for RIB + ET in IDFS linearly approached that of ET over a specified waning duration period. Specifically, the hazard rate for ribociclib was calculated as a weighted average of the hazard rate from the parametrized ribociclib IDFS curve and that of the ET only IDFS curve.

The weights were adjusted during each period of the specified waning duration such that the weight applied to the hazard rates of the ET only arm was equal to one at the end of the waning period.

It is difficult to assess if treatment effect waning should be included, and if so, when it should be introduced and for how long. With the current evidence from monarchE and NATALEE, no signs of treatment effect waning have been recorded. monarchE has 5-years follow-up data, with no signs of reduced efficacy. For NATALEE, there are now 4-years follow-up data available. Treatment with RIB + ET is indicated for up to three years, and thereby one additional year, when compared to abemaciclib in the same treatment setting (3 years with ribociclib vs 2 years with abemaciclib).

If abemaciclib and ribociclib are to be assessed equally, the relative weight of one year of follow-up in comparison to one additional year of treatment must be established. In the base case analysis, the two are assumed equal in importance. To mimic the assessment of abemaciclib for patients with HR+/HER2- eBC, treatment effect waning is assumed to begin 8 years after treatment initiation with waning lasting until the background mortality and IDFS are the same, as per the DMC assessment of abemaciclib (28). Below in Figure 31., the IDFS curve before and after application of treatment effect waning is presented.

Figure 31 40- and 15-year projection of parameterized curves (Gamma individual), with and without treatment effect waning applied to the RIB + ET arm and the parameterized curve for the ET only arm, curves are not adjusted for background mortality

ET: Endocrine therapy; K-M: Kaplan Meier

D.1.12 Time to treatment discontinuation

For patients receiving ribociclib and ET in combination, the model includes a time to treatment discontinuation (TTD) curve to estimate time on treatment with ribociclib and a separate TTD curve to estimate time on treatment with ET. This reflects a component of the trial design whereby patients who discontinued ribociclib or placebo could continue receiving treatment with ET. TTD was not a pre-defined endpoint in NATALEE and was calculated based on *post hoc* analyses of patient level exposure data. TTD was defined as the time from randomization until the last date of treatment exposure for patients who permanently discontinued for any reason, with events defined based on the following:

- Patient decision to discontinue treatment;
- Adverse event;
- Disease relapse;
- Endocrine therapy discontinuation;
- Physician decision;
- Lost to follow-up;
- Withdrawal from the study;
- Protocol deviation; and
- “Other”.

Patients who were still receiving treatment by the DCO date were censored for TTD at the date of censoring for IDFS.

Since the DCO of April 2024 occurred at the last treatment date of the last patient enrolled in NATALEE, the TTD of ribociclib was set equal to the KM of the TTD curve as all patients in NATALEE had finished treatment.

The model also includes an option to use individually fitted parametric curves to the TTD KM curves. The underlying statistics for the parametric fitting can be sent upon request and follow the same method as described for the extrapolated TTD curves for the ET treatment in both arms.

Probabilities of TTD events for ET treatment for patients receiving ET in combination with ribociclib, and ET only were estimated using patient-level data from the NATALEE trial. As ET can be administered for a maximum of five years, the duration of the NATALEE trial follow-up was not sufficient to capture all treatment discontinuation activities related to the use of ET. For this reason, parametric distributions were fitted to patient-level data on TTD.

KM survival and hazard rates by treatment group, the HR for RIB + ET versus ET only, and restricted mean survival time (RMST) by treatment group for all patients in the NATALEE trial are reported in Figure 32. Hazard rates for both treatment arms show a slight decreasing trend over time. The plot of time-dependent hazard ratios depicts hazard ratios that are on average close to one.

Figure 32 Time to Treatment Discontinuation of ET, by Randomized Treatment

A. Kaplan-Meier Survival Distribution

B. Hazard rates

C. Hazard ratio

D. Restricted Mean Survival Time

ET: endocrine therapy; ITT: intention to treat

A plot of a smoothed curve fit to Schoenfeld residuals of TTD for the ITT population of NATALEE is shown in Figure 33. The curve is virtually a straight line and the p-value on the test of non-proportionality is not significant, suggesting that the PH assumption is not unreasonable.

Figure 33 Plot of Smoothed Curve Fit to Schoenfeld Residuals for the TTD curve

HR: hazard ratio; TTD: time to treatment discontinuation

A ranking of parametric distributions fit to TTD by the fit statistics are shown in Table 68. The Weibull restricted distribution had the best fit based on all three statistics (AIC, AICc, and BIC).

Table 68 Fit Statistics for Parametric Distributions fit to ET only TTD curve

Distribution	AIC	AICc	BIC
Weibull (R)	[redacted]	[redacted]	[redacted]
Gamma (R)	[redacted]	[redacted]	[redacted]
Log-Logistic (R)	[redacted]	[redacted]	[redacted]
RCS Weibull (R)	[redacted]	[redacted]	[redacted]
Weibull (U)	[redacted]	[redacted]	[redacted]
Gen. Gamma (R)	[redacted]	[redacted]	[redacted]
Gamma (U)	[redacted]	[redacted]	[redacted]
RCS Lognormal (R)	[redacted]	[redacted]	[redacted]

Distribution	AIC	AICc	BIC
Log-Logistic (U)	[redacted]	[redacted]	[redacted]
RCS Log-Logistic (R)	[redacted]	[redacted]	[redacted]
Gen. F (R)	[redacted]	[redacted]	[redacted]
RCS Weibull (U)	[redacted]	[redacted]	[redacted]
Gen. Gamma (U)	[redacted]	[redacted]	[redacted]
Lognormal (R)	[redacted]	[redacted]	[redacted]
RCS Lognormal (U)	[redacted]	[redacted]	[redacted]
RCS Log-Logistic (U)	[redacted]	[redacted]	[redacted]
Lognormal (U)	[redacted]	[redacted]	[redacted]
Gen. F (U)	[redacted]	[redacted]	[redacted]
Gompertz (R)	[redacted]	[redacted]	[redacted]
Gompertz (U)	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]

AIC: Akaike information criterion, AICc: Aikaike information criterion corrected; BIC: Bayesian Information Criterion; R: restricted; U: unrestricted; TTD: time to treatment discontinuation; ITT: intention to treat; R: Restricted: U: Unrestricted.

Parametric survival distributions for TTD during the trial period for the best fitting distributions based on BIC are shown in Figure 34. The visual fit of the parametric distributions to the KM curves are all reasonably good.

Figure 34 Parametric Survival Distributions Fit to Ribociclib + ET and ET only TTD curve

Best fitting distributions based on BIC are shown. Distributions are ranks by BIC (left to right, top to bottom).
ET: Endocrine therapy; ITT: intention to treat; TTD: time to treatment discontinuation; R: Restricted; U: Unrestricted

Curve selection for TTD ET was 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 ET would be no longer than 5 years in the base case. The two best fitting models based on the BIC were the jointly fitted (i.e., restricted) Weibull and gamma distributions. Both models also had excellent visual fit to the observed TTD during follow-up. Given that treatment with ET in the economic model was assumed to last no longer than 5 years, consistent with the design of the NATALEE trial, either of these distributions would yield nearly identical results if used in the model. Based on these considerations and given that the Weibull restricted had better fit based on BIC, this distribution was selected for TTD ET in the base case.

Figure 35 Selected TTD curves for NSAI treatment with Ribociclib + ET and ET only and Kaplan Meier curves

D.1.13 Cure-point

Not applicable

D.2 ET-Resistant

Patients with metastatic recurrence ≤12 months from completing adjuvant ET were assumed to enter the ET-resistant DR substate. Survival curves for the ET-resistant substate were estimated using patient-level data for Group B of the MONALEESA-3 trial (DCO June 2019). MONALEESA-3 compared ribociclib plus fulvestrant versus fulvestrant alone in men and postmenopausal women with HR+/HER2- advanced breast cancer and who have received no more than one prior ET for advanced disease. Group B (n = 346) included patients with relapse on or within 12 months from completion of [neo]adjuvant ET and no ET for aBC (n = 207) and those with one prior line of ET for aBC (n = 139).

For patients receiving ribociclib plus fulvestrant, extrapolated survival curves for PFS, OS, and TTD were estimated by fitting parametric survival distributions to individual patient data for the ribociclib arm of MONALEESA-3 Group B. For abemaciclib and palbociclib combination therapies, PFS, OS, and TTD were assumed to be the same as for ribociclib plus fulvestrant since they all are CDK4/6 inhibitors. It has come to light, that palbociclib has inferior overall survival outcomes and this assumption is therefore not true to effectiveness observed in the real-life setting. However, the use of palbociclib for new patients is miniscule and will not impact the overall results in any meaningful way. For patients receiving other treatments, survival curves were estimated by applying estimated HRs for PFS and OS for the given comparator versus PFS and OS for ribociclib plus

fulvestrant to the corresponding survival curve for ribociclib plus fulvestrant. HRs for PFS and OS for other comparators versus ribociclib plus fulvestrant were estimated based on an ITC of treatments for HR+/HER2-aBC. For Everolimus plus exemestane, TTD was estimated by applying a HR based on Cox PH regression of TTD versus PFS from BOLERO-2 (HR = 1.27; 95% CI: 1.01, 1.67). For monotherapies in the ET-resistant substate, treatment was assumed to continue until disease progression. Extrapolated survival curves and results of the ITC are described in the following sections.

D.2.1 PFS Extrapolations

Kaplan-Meier survival distribution for ribociclib with fulvestrant and fulvestrant for ET-resistant patients based on Group B in MONALEESA-3 are reported in Figure 36. This outcome was estimated using the January 12, 2022, DCO of MONALEESA-3 with a median follow-up time of 70.8 months. The curves diverge at about 3 months with PFS for ribociclib with fulvestrant higher relative to fulvestrant; this trend continues until the end of the follow-up period.

Figure 36 Kaplan-Meier Survival Distribution for Progression-Free Survival in ET-Resistant Patients based on Group B of MONALEESA-3, by Randomized Treatment.

RIB: Ribociclib

A ranking of parametric distributions fit to PFS by the fit statistics are shown in Table 69. The best fitting distributions, according to BIC statistic were as follows:

- Lognormal restricted;
- Lognormal unrestricted;
- Generalized gamma restricted;
- RCS Log-normal restricted;
- Log-Logistic restricted; and
- Generalized F restricted.

The top fitting distributions based on the AIC and AICc are generally similar to those based on the BIC. BIC generally penalizes complex models with many parameters to a higher extend. [redacted].

Table 69 Fit Statistics for Parametric Distributions fit to PFS for ET-Resistant Patients based on Group B of MONALEESA-3

Distribution	AIC	AICc	BIC
Lognormal (R)	[redacted]	[redacted]	[redacted]
Lognormal (U)	[redacted]	[redacted]	[redacted]
Gen. Gamma (R)	[redacted]	[redacted]	[redacted]
RCS Log-normal (R)	[redacted]	[redacted]	[redacted]
Log-Logistic (R)	[redacted]	[redacted]	[redacted]
Gen. F (R)	[redacted]	[redacted]	[redacted]
RCS Weibull (R)	[redacted]	[redacted]	[redacted]
Gen. Gamma (U)	[redacted]	[redacted]	[redacted]
Log-Logistic (U)	[redacted]	[redacted]	[redacted]
RCS Log-normal (U)	[redacted]	[redacted]	[redacted]
RCS Log-Logistic (R)	[redacted]	[redacted]	[redacted]
Gompertz (R)	[redacted]	[redacted]	[redacted]
Gompertz (U)	[redacted]	[redacted]	[redacted]
RCS Weibull (U)	[redacted]	[redacted]	[redacted]
Gen. F (U)	[redacted]	[redacted]	[redacted]
RCS Log-Logistic (U)	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]
Weibull (R)	[redacted]	[redacted]	[redacted]
Weibull (U)	[redacted]	[redacted]	[redacted]

D.2.2 OS Extrapolations

Membership in the PPS state when using the PSM approach was calculated as the difference between PFS and OS; this approach therefore relies on survival curves for OS.

For patients receiving ribociclib plus fulvestrant and fulvestrant monotherapy, probabilities of OS were estimated using a similar approach employed for the estimation of PFS described above. Specifically, OS was estimated by fitting parametric survival distribution to the individual patient data from MONALEESA-3. Parametric survival distributions fitted to OS data were evaluated using the same methodology employed for PFS to select the most appropriate model.

Kaplan-Meier survival distributions by treatment group for ET-resistant patients based on Group B of MONALEESA-3 are reported in Figure 37. The plot shows there is a consistent divergence in survival by treatment pattern with OS for ribociclib with fulvestrant higher relative to fulvestrant.

Figure 37 Kaplan-Meier Survival Distribution for Overall Survival in ET-Resistant Patients based on Group B of MONALEESA-3, by Randomized Treatment

Ribo: ribociclib

A ranking of parametric distributions fit to PFS by the fit statistics are shown in Table 70 The best fitting distributions, according to BIC statistic were as follows:

- Log-Logistic restricted;
- Weibull restricted;
- RCS Log-normal restricted;
- Generalized Gamma restricted;
- RCS Log-Logistic restricted; and
- RCS Weibull restricted.

The top fitting distributions based on the AIC and AICc are generally similar to those based on the BIC.

Table 70 Fit Statistics for Parametric Distributions fit to OS for ET-Resistant Patients based on Group B of MONALEESA-3

Distribution	AIC	AICc	BIC
Log-Logistic (R)	[redacted]	[redacted]	[redacted]
Weibull (R)	[redacted]	[redacted]	[redacted]
RCS Log-normal (R)	[redacted]	[redacted]	[redacted]
Gen. Gamma (R)	[redacted]	[redacted]	[redacted]
RCS Log-Logistic (R)	[redacted]	[redacted]	[redacted]
RCS Weibull (R)	[redacted]	[redacted]	[redacted]
Log-Logistic (U)	[redacted]	[redacted]	[redacted]
Weibull (U)	[redacted]	[redacted]	[redacted]
Lognormal (R)	[redacted]	[redacted]	[redacted]
Gen. F (R)	[redacted]	[redacted]	[redacted]
Gompertz (R)	[redacted]	[redacted]	[redacted]
Lognormal (U)	[redacted]	[redacted]	[redacted]
RCS Log-normal (U)	[redacted]	[redacted]	[redacted]
Gen. Gamma (U)	[redacted]	[redacted]	[redacted]
RCS Weibull (U)	[redacted]	[redacted]	[redacted]
RCS Log-Logistic (U)	[redacted]	[redacted]	[redacted]
Gompertz (U)	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]
Gen. F (U)	[redacted]	[redacted]	[redacted]

RCS: Restricted cubic spline; AIC: Akaike information criterion, AICc: AIC corrected; BIC: Bayesian Information Criterion; U: unrestricted; R: Restricted

D.2.3 Indirect Treatment Comparisons of PFS and OS for ET-Resistant aBC

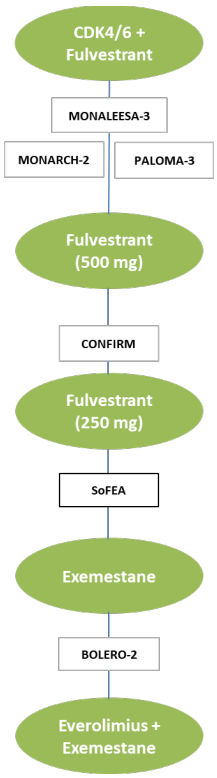
Estimates of relative treatment effects for the ET-Resistant substate were based on ITCs of PFS and OS used in economic evaluations of CDK4/6 inhibitors in combination with fulvestrant as treatment for advanced breast cancer. Specifically, trials included in the ITC were based on a network meta-analysis (NMA) in TA687 of ribociclib plus fulvestrant as

treatment for HR+/HER2- advanced breast cancer (101). The NMA in TA687 was informed by patient level data from Group B of MONALEESA-3, which aligns closely with the definition of ET-Resistant distant recurrence used in the economic model described herein (50). Point estimates for treatment effects were updated with the latest reported data cutoffs for each RCT included in the original ITC, identified by a systematic literature review (SLR) commissioned by Novartis (Data on file). The search strategy and findings of the SLR are described in a separate report (Data on file). Briefly, an SLR was first conducted in 2018 to identify RCTs that evaluated comparators of interest as treatment for HR+/HER2- advanced breast cancer (102). An updated SLR was then conducted in September 2024, and reports of extended follow-up for RCTs identified in the original SLR were extracted. The ITCs of PFS and OS were then conducted using the latest data from each RCT. Comparators of interest for each of the DR substates were based on a survey of Canadian clinicians (49). The usage was later adapted to reflect expected usage in Denmark based on KOL input. The original identified and included treatments were:

- Ribociclib plus fulvestrant;
- Palbociclib plus fulvestrant;
- Abemaciclib plus fulvestrant;
- Fulvestrant;
- Everolimus plus exemestane;
- Exemestane;
- Tamoxifen; and
- Capecitabine.

Six RCTs evaluating at least one comparator of interest for the ET-Resistant population were included, forming a connected evidence network, as shown in Figure 38. For 3 of the included RCTs, MONALEESA-3, MONARCH-2, and PALOMA-3, the SLR identified reports of later data cutoffs than those available at the time of the aforementioned TA687 (50, 53, 103). The remaining 3 RCTs were CONFIRM, SoFEA, and BOLERO-2, allowing for everolimus plus exemestane and exemestane monotherapy to be connected to the evidence network (57-59). Trials and point estimates used in the ITCs of PFS and OS are summarized in Table 71.

Figure 38 Network Diagram: ITCs of PFS and OS for ET-Resistant Distant Recurrence



ITC: Indirect treatment comparison, PFS: Progression-free survival; OS: Overall survival; ET: Endocrine therapy; CDK 4/6 cyclin dependent kinase 4/6.

Sources of clinical and methodological heterogeneity among study populations were identified, which may have introduced bias to the ITCs. Importantly, there were differences in study populations between the 3 trials that evaluated CDK4/6 inhibitors. Data from MONALEESA-3 used in the ET-Resistant ITC were based on the Group B subgroup (i.e., the ITT population of MONALEESA-3 included both ET-sensitive and ET-resistant patients) (104). Imbalances in baseline characteristics between the Group B subgroup of MONALEESA-3 and the PALOMA-3 and MONARCH-2 trials were considered to be likely sources of bias for the ITC (56, 105). Considering these limitations with the comparison of ribociclib versus the other CDK4/6 inhibitors in the ET-Resistant setting, the ITC assumed HRs of 1.0 for palbociclib and abemaciclib versus ribociclib in the base case. Results of the ITC based on the HRs from the corresponding trials of each CDK4/6 inhibitor are also presented in this report, but these should be interpreted with caution as they are subject to a high degree of uncertainty.

Additionally, the BOLERO-2 trial included patients receiving first-, second-, and third line+ treatment, whereas the MONALEESA-3 trial did not enroll patients receiving later than second-line (76, 106). For the CONFIRM trial of fulvestrant 500mg versus fulvestrant 250mg, HER2 status was not evaluated and the proportion of patients with HER2- breast cancer in this trial is unknown (57). In SoFEA, 57% of patients were HER2- while 7% HER2+ and 36% had unknown HER2-receptor status (58). These limitations are considered to be sources of potential bias that should be considered when interpreting results of the ITC. Direct estimates of treatment effects for PFS and OS used as inputs are shown in Table 71.

Table 71 HRs for PFS and OS Used in the ITC of ET-Resistant aBC Patients

Trial (Subgroup)	Study Arm		HR (95%CI)	
	Experimental	Control	PFS	OS
MONALEESA-3 (50)	Ribociclib + Fulvestrant 500 mg	Fulvestrant 500 mg	[redacted]	[redacted]
PALOMA-3 (53, 54)	Palbociclib + Fulvestrant 500 mg	Fulvestrant 500 mg	[redacted]	[redacted]
MONARCH-2 (55, 56)	Abemaciclib + Fulvestrant 500 mg	Fulvestrant 500 mg	[redacted]	[redacted]
CONFIRM (57)	Fulvestrant 500 mg	Fulvestrant 250 mg	[redacted]	[redacted]
SoFEA (58)	Fulvestrant 250 mg	Exemestane	[redacted]	[redacted]
BOLERO-2 (59)	Everolimus + Exemestane	Exemestane	[redacted]	[redacted]

NSAI: Nonsteroidal aromatase inhibitor; PFS: Progression-Free Survival; OS: Overall Survival; CI: Credible interval; N/A: not applicable; HR: Hazard ratio

ITCs were calculated using a frequentists approach, i.e., Bucher method (107). With this approach, the effect of intervention B relative to intervention A can be estimated indirectly as follows, using the direct estimators for the effects of intervention C relative to intervention A (EffectAC) and intervention C relative to intervention B ($Effect_{BC}$):

$Effect_{AB} = Effect_{AC} – Effect_{BC}$

The variance of the indirect estimator EffectAB is the sum of the variances of the direct estimators:

$Variance_{AB} = Variance_{AC} + VarianceBC$

The corresponding two-tailed 95% confidence interval can thus be calculated as follows:

$Effect_{AB} \pm Z_{0.975} \times Variance_{AB}^{1/2}$

As there were no multi-arm trials and no closed loops in the evidence network, the conduct of the ITC using the Bucher method with treatment effects expressed as HRs was considered appropriate. For direct comparisons involving more than one trial, pooled HRs for these direct comparisons were estimated using fixed or random effects meta-analysis (108). Given that no trials of letrozole, anastrozole, TAM, or capecitabine were included in the evidence network, HRs for PFS and OS for these comparators were assumed to be

based on exemestane. Results of the ITCs of PFS and OS for ET-resistant aBC are shown as HRs for each comparator versus ribociclib plus fulvestrant in Table 72.

Table 72 Base Case Results of ITCs for PFS and OS in the ET-Resistant State

Comparator	HR (95%CI) vs. Ribociclib + Fulvestrant	
	Progression-Free Survival	Overall Survival
Fulvestrant 500 mg	[redacted]	[redacted]
Ribociclib + Fulvestrant	[redacted]	[redacted]
Palbociclib + Fulvestrant	[redacted]	[redacted]
Abemaciclib + Fulvestrant	[redacted]	[redacted]
NSAI*	[redacted]	[redacted]
Exemestane	[redacted]	[redacted]
Everolimus + Exemestane	[redacted]	[redacted]
Tamoxifen*	[redacted]	[redacted]
Capecitabine*	[redacted]	[redacted]

*Assumed to be the same as exemestane; NSAI: Nonsteroidal aromatase inhibitor; PFS: Progression-Free Survival; OS: Overall Survival; CI: Credible interval; N/A: not applicable; HR: Hazard ratio

As stated above, the HRs for PFS and OS versus ribociclib for palbociclib and abemaciclib in the ET-Resistant setting were assumed to be 1.0 due to heterogeneity in the study populations that evaluated these therapies. Results of the ITCs using the HRs for PFS and OS from the MONARCH-2 and PALOMA-3 trial are presented for completeness in Table 73; however, these estimates should be interpreted with caution.

Table 73 Alternative Results of ITCs for CDK4/6 Inhibitors in ET-Resistant Patients

Comparator	**HR (95%CI) vs. Ribociclib + Fulvestrant**	
	Progression-Free Survival	Overall Survival
Palbociclib + Fulvestrant	[redacted]	[redacted]
Abemaciclib + Fulvestrant	[redacted]	[redacted]

NSAI: Nonsteroidal aromatase inhibitor; PFS: Progression-Free Survival; OS: Overall Survival; CI: Credible interval; N/A: not applicable; HR: Hazard ratio

D.2.4 TTD Extrapolations

Probabilities of remaining on ribociclib or blinded placebo treatment (and the complemental probabilities of discontinuation) for ET-resistant patients were estimated using individual patient failure time data from MONALEESA-3 using methods similar to those described above for PFS and PPS. In particular, survival distributions for time-to-treatment discontinuation or death (TTD) for ribociclib or placebo and for fulvestrant were estimated separately for patients randomized to ribociclib plus fulvestrant and fulvestrant monotherapy. For the former group, TTD was estimated separately for ribociclib and fulvestrant. TTD was defined as time from randomization to discontinuation of medication or death, whichever occurred first, with patients who did not discontinue or die censored

at censoring time for OS. In the base case, it is assumed that TTD for ribociclib or fulvestrant cannot exceed the PFS (i.e., PFS is used as a ceiling for TTD).

A comparison of the Kaplan-Meier survival distributions for PFS for ribociclib plus fulvestrant and fulvestrant versus TTD of ribociclib and blinded placebo among ET-resistant patients based on Group B of MONALEESA-3 is shown in Figure 39. TTD for ribociclib is well below the PFS curve for the ribociclib plus fulvestrant group throughout follow-up, although it approaches PFS towards the end of follow-up. There is not much separation between the curves for TTD for blinded placebo and PFS for the fulvestrant treatment group.

Figure 39 Comparison of PFS and TTD of Ribociclib and Blinded Placebo for Patients in ET-Resistant Patients based on Group B of MONALEESA-3, by Randomized Treatment

PFS: progression-free survival; TTD: Time to treatment discontinuation

Kaplan-Meier survival distributions for TTD for ribociclib and blinded placebo for patients in Group B are reported in Figure 40.

Figure 40 Kaplan-Meier Survival Distribution for TTD for Ribociclib or Blinded Placebo for Patients in ET-Resistant Patients based on Group B of MONALEESA-3, by Randomized Treatment

Ribo: ribociclib

A ranking of parametric distributions fit to TTD by the fit statistics are shown in Table 74. The best fitting distributions, according to BIC statistic were as follows:

- Gompertz restricted;
- RCS Weibull restricted;
- Generalized Gamma restricted;
- Gompertz unrestricted;
- RCS Log-normal restricted; and
- Generalized F restricted.

The top fitting distributions based on the AIC and AICc are generally like those based on the BIC. .

The TTD for other CDK 4/6s were assumed equal to that of ribociclib out of simplicity.

Table 74 Fit Statistics for Parametric Distributions fit to TTD for ET-Resistant Patients based on Group B of MONALEESA-3

Distribution	AIC	AICc	BIC
Gompertz (R)	[redacted]	[redacted]	[redacted]
RCS Weibull (R)	[redacted]	[redacted]	[redacted]
Gen. Gamma (R)	[redacted]	[redacted]	[redacted]
Gompertz (U)	[redacted]	[redacted]	[redacted]
RCS Log-normal (R)	[redacted]	[redacted]	[redacted]
Gen. F (R)	[redacted]	[redacted]	[redacted]
RCS Weibull (U)	[redacted]	[redacted]	[redacted]
Gen. Gamma (U)	[redacted]	[redacted]	[redacted]
RCS Log-normal (U)	[redacted]	[redacted]	[redacted]
RCS Log-Logistic (R)	[redacted]	[redacted]	[redacted]
RCS Log-Logistic (U)	[redacted]	[redacted]	[redacted]
Gen. F (U)	[redacted]	[redacted]	[redacted]

RCS: Restricted cubic spline; AIC: Akaike information criterion, AICc: AIC corrected; BIC: Bayesian Information Criterion; U: unrestricted; R: Restricted

D.3 ET-Sensitive

Patients with metastatic recurrence >12 months after completing adjuvant ET were assumed to enter the ET-sensitive DR substate. Survival curves for the ET-sensitive substate were estimated using patient-level data from the MONALEESA-2 trial (DCO June 2021).

For patients receiving ribociclib plus AI, extrapolated survival curves for PFS, OS, and TTD were estimated by fitting parametric survival distributions to individual patient data for the ribociclib arm of MONALEESA-2. For abemaciclib and palbociclib combination therapies, PFS, OS, and TTD were assumed to be the same as for ribociclib plus AI give that they are all CDK4/6 inhibitors. For patients receiving other treatments, survival curves were estimated by applying estimated HRs for PFS and OS for the given comparator versus PFS and OS for ribociclib plus AI to the corresponding survival curve for ribociclib plus AI.

D.3.1 PFS Extrapolations

A plot showing the log cumulative hazard versus log-time for PFS assessed by the study investigators is shown in Figure 41. The hazards plot shows crossing of the curves during the first two months. From month 2 to the end of study follow-up, the hazard curves are parallel indicating that proportional hazards hold for this period. The initial crossing of the curves, and hence lack of proportionality across the entire period, indicates that a proportional hazards model fitted to both arms of the study and containing a variable for treatment group would not be appropriate.

Figure 41 Assessment of Proportional Hazards for PFS in MONALEESA-2

Given this evidence that the PH assumption appeared to be unreasonable, a series of independent models were fitted to patient-level data from each arm of MONALEESA-2. This included conventional survival models and the Royston Parmar cubic spline model (proportional hazards configuration). As shown in

Table 75, the best-fitting distributions according to BIC were the exponential, lognormal, generalized gamma and log-logistic.

Table 75 Fit Statistics for Analysis of PFS in MONALEESA-2

Distribution	Placebo plus letrozole		Distribution	Ribociclib plus letrozole	
	AIC	BIC		AIC	BIC
Spline 5 knot	[redacted]	[redacted]	Lognormal	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	Generalized gamma	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	Log-logistic	[redacted]	[redacted]
Spline 3 knot	[redacted]	[redacted]	Spline 1 knot	[redacted]	[redacted]
Spline 4 knot	[redacted]	[redacted]	Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	Exponential	[redacted]	[redacted]
Spline 1 knot	[redacted]	[redacted]	Spline 2 knot	[redacted]	[redacted]
Spline 2 knot	[redacted]	[redacted]	Spline 3 knot	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	Weibull	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	Gamma	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	Spline 4 knot	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	Spline 5 knot	[redacted]	[redacted]

Visual comparisons of individually fitted parametric distributions to PFS for the ribociclib arm of MONALEESA-2 are shown in Figure 42. During trial follow-up, all the fitted curves appear to have excellent visual fit to the observed K-M survival. There appear to be slight variations in projected PFS after follow-up for the different models.

Figure 42 Parametric Survival Distributions Individually fit to PFS in ET-Sensitive Patients based on MONALEESA-2, Ribociclib Arm

[redacted] in the base case because it had the 2nd best statistical fit based on BIC, had excellent visual fit to the observed K-M curve for ribociclib, and had higher projected long-term PFS than some of the outliers, including the exponential and Weibull models. The exponential had the best statistical fit based on BIC; however, it also had the lowers projection of PFS beyond the observed period in MONALEESA-2. The lognormal model was favored over the exponential for the base case because it was expected that long-term PFS for the ET-sensitive state would not be lower than for the ET-resistant state. [redacted].

D.3.2 OS Extrapolations

A plot showing the log cumulative hazard versus log-time for OS assessed by the study investigators is shown in Figure 43. The hazards plot shows crossing of the curves at approximately month 5 and month 10. Beyond month 10, no crossing of curves is observed, and the curves become parallel. Lack of proportionality across the entire period indicates that a proportional hazards model fitted to both arms of the study and containing a variable for treatment group would not be appropriate.

Figure 43 Assessment of Proportional Hazards for OS in MONALEESA-2

PBO: Placebo; ribo600: Ribociclib 600mg; LET: letrozol 2.5mg

Fit statistics for individually fitted parametric distributions are shown in Table 76. The best-fitting model according to BIC was the log-logistic, followed by the gamma and Weibull models.

Table 76 Fit Statistics for Analysis of OS in MONALEESA-2

Distribution	Placebo plus letrozole		Distribution	Ribociclib plus letrozole	
	AIC	BIC		AIC	BIC
Log-logistic					
Gamma					
Generalized gamma					
Spline 1 knot					
Weibull					
Spline 2 knot					
Spline 4 knot					
Spline 3 knot					
Spline 5 knot					
Lognormal					
Gompertz					
Exponential					

AIC: Akaike information criterion; BIC: Bayesian information criterion

Visual comparisons of individually fitted parametric distributions to OS for the ribociclib arm of MONALEESA-2 are shown in Figure 44. The log-logistic model, which had the best statistical fit based on the BIC, appeared to also have excellent visual fit to K-M OS during

the trial period. There was relatively wide variation in the projected OS after the trial period for the fitted models. XX [redacted].

Figure 44 Parametric Survival Distributions Individually fit to OS in ET-Sensitive Patients based on MONALEESA-2, Ribociclib Arm

The log-logistic distribution fit to OS was selected for use in the base case. This model had excellent visual fit to the observed K-M OS, best statistical fit based on the BIC, and projected long-term OS that was intermediate among the standard distributions.

D.3.3 Indirect Treatment Comparisons of PFS and OS for ET-Sensitive aBC

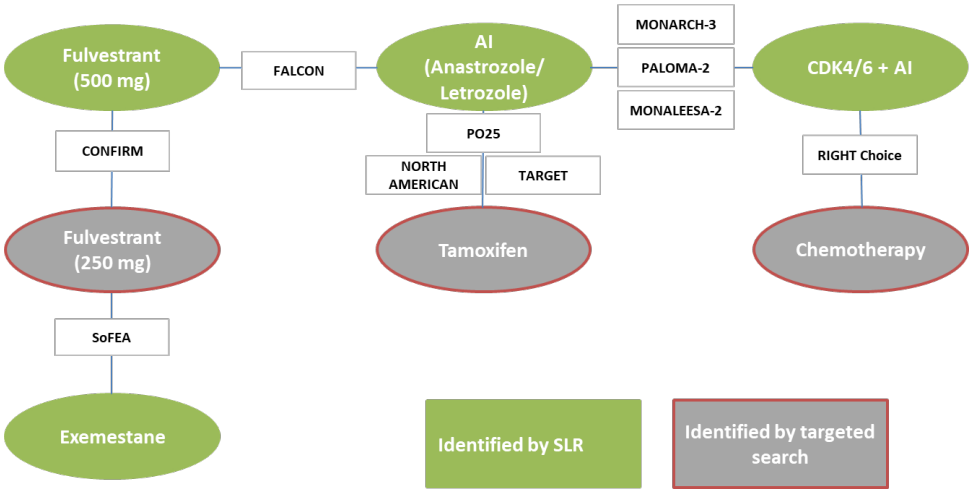
RCTs for the ITCs of PFS and OS for the ET-sensitive substate were identified by an SLR commissioned by Novartis (Data on file). Comparators of interest for ET-Sensitive advanced breast cancer were based on a survey of Canadian clinicians (109), and included:

- Ribociclib plus NSAI;
- Palbociclib plus NSAI;
- Abemaciclib plus NSAI;
- Fulvestrant;
- Letrozole;
- Anastrozole;
- Exemestane;
- Tamoxifen;
- Paclitaxel; and
- Docetaxel

The SLR identified 5 trials for the ITC of ET-sensitive aBC: MONALEESA-2, PALOMA-2, MONARCH-3, SoFEA, and FALCON (58, 60, 62-64). However, these trials only evaluated CDK4/6 inhibitors, AIs, and fulvestrant. A supplementary targeted literature search was therefore conducted to include additional comparators of interest in the evidence network. The supplementary search identified another 5 trials, allowing for TAM and

chemotherapies to be connected to the evidence network: P025, NORTH AMERICAN, TARGET, CONFIRM, and RIGHT Choice (57, 65-68, 110). The network diagram for the ITC is shown in Figure 45.

Figure 45 Network Diagram: ITCs of PFS and OS for ET-sensitive Distant Recurrence



CDK 4/6: Cyclin dependent kinase; AI: Aromatase inhibitor

As with the ITC for the ET-Resistant state, the ITC for the ET-sensitive setting assumed HRs of 1.0 for palbociclib and abemaciclib versus ribociclib in the base case. Limitations of the ITC should be noted. As stated above, 5 of the trials included in the ITC were identified by non-systematic literature searches. Additionally, there was heterogeneity in study populations across the RCTs included in the network. These factors may have introduced bias to the ITCs, and the results should therefore be interpreted with caution. Direct estimates of treatment effects for PFS and OS are shown in Table 77.

Table 77 HRs for PFS and OS Used in the ITC of ET-Sensitive ABC Patients

Trial	Study Arm		HR (95%CI)	
	Experimental	Control	PFS	OS
MONALEESA-2 (60)	Ribociclib + NSAI	NSAI	[redacted]	[redacted]
PALOMA-2 (61, 62)	Palbociclib + NSAI	NSAI	[redacted]	[redacted]
MONARCH-3 (63)	Abemaciclib + NSAI	NSAI	[redacted]	[redacted]
CONFIRM (57)	Fulvestrant 500 mg	Fulvestrant 250 mg	[redacted]	[redacted]
SoFEA (58)	Fulvestrant 250 mg	Exemestane	[redacted]	[redacted]
FALCON (64)	Fulvestrant 500 mg	NSAI	[redacted]	[redacted]
PO25 (65)	NSAI	Tamoxifen	[redacted]	[redacted]
North American (66)	Tamoxifen	NSAI	[redacted]	[redacted]

TARGET (67)	Tamoxifen	NSAI	[redacted]	[redacted]
RIGHT Choice (68)	Ribociclib + NSAI	Chemotherapy*	[redacted]	[redacted]

*Chemotherapy arm consisted of combination regimens based on investigator discretion (NSAI: Nonsteroidal aromatase inhibitor; PFS: Progression-Free Survival; OS: Overall Survival; CI: Credible interval; N/A: not applicable; HR: Hazard ratio

ITCs were calculated using a frequentists approach, i.e., Bucher method (107), consistent with the ET-Resistant ITCs. In the base case, the HRs for PFS and OS versus ribociclib for palbociclib and abemaciclib in the ET-Sensitive setting were assumed to be 1.0 due to heterogeneity in the study populations that evaluated these therapies.

Table 78. Base Case Results of ITCs for PFS and OS in the ET-Sensitive State

Comparator	HR (95%CI) vs. Ribociclib + NSAI	
	Progression-Free Survival	Overall Survival
Ribociclib + NSAI	[redacted]	[redacted]
Palbociclib + NSAI	[redacted]	[redacted]
Abemaciclib + NSAI	[redacted]	[redacted]
Fulvestrant	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]
NSAI	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]
Exemestane	[redacted]	[redacted]

NSAI: Nonsteroidal aromatase inhibitor; PFS: Progression-Free Survival; OS: Overall Survival; CI: Credible interval; N/A: not applicable

Results of the ITCs using the HRs for PFS and OS from the MONARCH-3 and PALOMA-2 trials are presented for completeness in Table 79; However, these estimates should be interpreted with caution.

Table 79 Alternative Results of ITCs for CDK4/6 Inhibitors in ET-Sensitive Patients

Comparator	HR (95%CI) vs. Ribociclib + NSAI	
	Progression-Free Survival	Overall Survival
Palbociclib + NSAI	[redacted]	[redacted]
Abemaciclib + NSAI	[redacted]	[redacted]

NSAI: Nonsteroidal aromatase inhibitor; PFS: Progression-Free Survival; OS: Overall Survival; CI: Credible interval; N/A: not applicable; HR: Hazard ratio

D.3.4 TTD Extrapolations

The duration of treatment for ribociclib in the ET-sensitive state was modelled using patient-level data for TTD from the MONALEESA-2 study. Fit statistics for parametric distributions are shown in Table 80. The best-fitting models according to BIC included the Weibull, Gompertz, and gamma models.

Table 80 Fit Statistics for Analysis of TTD in MONALEESA-2

Distribution	AIC	BIC
Generalized gamma	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]
Exponential	[redacted]	[redacted]

AIC: Aikaike information criterion; BIC: Bayesian information criterion

A visual comparison of projected TTD for the fitted distribution against K-M TTD is shown in Figure 46. During the trial period, all the fitted curves appeared to have reasonably good visual fit to the K-M TTD. After the trial period, long-term projections for the different models appeared to be similar, except for the log-logistic and lognormal models, which projected TTD moderately higher than the other models.

Figure 46 Parametric Survival Distributions Individually fit to TTD in ET-Sensitive Patients based on MONALEESA-2, Ribociclib Arm

[redacted]

Data on TTD were nearly complete by the time of DCO (93% of patients had discontinued ribociclib). As such, consideration of plausibility and visual fit were prioritized fit statistics. In terms of plausibility, it was believed that a constant hazard beyond the trial period was the most appropriate characterization of the hazard rate for TTD given that data on TTD were 93% complete. The exponential distribution had very good visual fit to the observed KM TTD and is characterized by constant hazards. [redacted]. The TTD for other CDK 4/6s were assumed equal to that of ribociclib out of simplicity.

Appendix E. Serious adverse events

In the table below, we present the serious adverse events reported at the 29 April 2024 data cut-off from the safety set.

Table 81 Serious adverse events, regardless of study drug relationship, by preferred term (at least 0.2 percent incidence for all grades in either group). Source: data on file (9).

	ET + Ribociclib, N=2,526				ET Only, N=2,441			
	All grades n (%)	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**All Grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
Number of patients with at least one SAE	375 (14.8)	267 (10.6)	47 (1.9)	11 (0.4)	267 (10.9)	204 (8.4)	26 (1.1)	4 (0.2)
COVID-19	20 (0.8)	13 (0.5)	0	3 (0.1)	13 (0.5)	9 (0.4)	0	1 (<0.1)
Pulmonary embolism	15 (0.6)	11 (0.4)	1 (<0.1)	2 (0.1)	5 (0.2)	5 (0.2)	0	0
Pneumonia	14 (0.6)	12 (0.5)	0	0	10 (0.4)	8 (0.3)	0	0
Dyspnoea	12 (0.5)	9 (0.4)	0	0	5 (0.2)	3 (0.1)	0	0
Alanine aminotransferase increased	9 (0.4)	1 (<0.1)	7 (0.3)	0	0	0	0	0
Breast cellulitis	9 (0.4)	9 (0.4)	0	0	3 (0.1)	3 (0.1)	0	0

	ET + Ribociclib, N=2,526				ET Only, N=2,441			
COVID-19 pneumonia	9 (0.4)	5 (0.2)	0	3 (0.1)	5 (0.2)	4 (0.2)	1 (<0.1)	0
Cellulitis	8 (0.3)	8 (0.3)	0	0	6 (0.2)	6 (0.2)	0	0
Humerus fracture	8 (0.3)	7 (0.3)	0	0	4 (0.2)	3 (0.1)	0	0
Atrial fibrillation	7 (0.3)	5 (0.2)	1 (<0.1)	0	8 (0.3)	7 (0.3)	0	0
Cholelithiasis	7 (0.3)	6 (0.2)	1 (<0.1)	0	6 (0.2)	6 (0.2)	0	0
Papillary thyroid cancer	7 (0.3)	7 (0.3)	0	0	2 (0.1)	2 (0.1)	0	0
Pyrexia	7 (0.3)	2 (0.1)	0	0	1 (<0.1)	1 (<0.1)	0	0
Urinary tract infection	7 (0.3)	7 (0.3)	0	0	3 (0.1)	3 (0.1)	0	0
Cerebrovascular accident	6 (0.2)	2 (0.1)	1 (<0.1)	0	1 (<0.1)	0	1 (<0.1)	0
Drug-induced liver injury	6 (0.2)	2 (0.1)	3 (0.1)	0	0	0	0	0

	ET + Ribociclib, N=2,526				ET Only, N=2,441			
Aspartate aminotransferase increased	5 (0.2)	2 (0.1)	3 (0.1)	0	0	0	0	0
Diarrhoea	5 (0.2)	3 (0.1)	0	0	0	0	0	0
Hepatotoxicity	5 (0.2)	3 (0.1)	2 (0.1)	0	0	0	0	0
Osteoarthritis	5 (0.2)	4 (0.2)	0	0	5 (0.2)	5 (0.2)	0	0
Postoperative wound infection	5 (0.2)	5 (0.2)	0	0	2 (0.1)	2 (0.1)	0	0
Acute myocardial infarction	4 (0.2)	1 (<0.1)	3 (0.1)	0	0	0	0	0
Appendicitis	4 (0.2)	3 (0.1)	1 (<0.1)	0	2 (0.1)	2 (0.1)	0	0
Erysipelas	4 (0.2)	2 (0.1)	0	0	3 (0.1)	3 (0.1)	0	0
Hypertension	4 (0.2)	3 (0.1)	0	0	3 (0.1)	2 (0.1)	0	0
Mastitis	4 (0.2)	2 (0.1)	0	0	2 (0.1)	2 (0.1)	0	0
Pneumonia viral	4 (0.2)	0	0	0	3 (0.1)	1 (<0.1)	0	0

	ET + Ribociclib, N=2,526				ET Only, N=2,441			
Suspected COVID-19	4 (0.2)	0	0	0	1 (<0.1)	0	0	0
Syncope	4 (0.2)	4 (0.2)	0	0	2 (0.1)	2 (0.1)	0	0
Cataract	2 (0.1)	0	0	0	4 (0.2)	3 (0.1)	0	0

Table note: Preferred terms are sorted in descending frequency based on frequency in ET + ribociclib arm. MedDRA Version 27.0 has been used for reporting.

Appendix F. Health-related quality of life

Not applicable.

Appendix G. Probabilistic sensitivity analyses

Table 82 Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Settings				
Age	60	38.91	81.08	Normal
Probabilities				
IDFS distribution RIB + ET: Gamma (i)				
Parameter 1	[redacted]	[redacted]	[redacted]	[redacted]
Parameter 2	[redacted]	[redacted]	[redacted]	[redacted]
IDFS distribution ET: Gamma (i)				
Parameter 1	[redacted]	[redacted]	[redacted]	[redacted]
Parameter 2	[redacted]	[redacted]	[redacted]	[redacted]
TTD distribution RIB + ET: Gamma (i)				
Type of event from NMR state, RIB + ET				
% of events that are deaths	[redacted]	[redacted]	[redacted]	[redacted]
% of events that are DR	[redacted]	[redacted]	[redacted]	[redacted]
% of events that are SPM	[redacted]	[redacted]	[redacted]	[redacted]
% of events that are NMR	[redacted]	[redacted]	[redacted]	[redacted]
Type of event from NMR state, RIB + ET				
% of events that are deaths	[redacted]	[redacted]	[redacted]	[redacted]
% of events that are DR	[redacted]	[redacted]	[redacted]	[redacted]
% of events that are SPM	[redacted]	[redacted]	[redacted]	[redacted]
% of events that are NMR	[redacted]	[redacted]	[redacted]	[redacted]
TTD NSAI RIB+ET: Weibull (R)				

Parameter 1	[redacted]	[redacted]	[redacted]	[redacted]
Parameter 2	[redacted]	[redacted]	[redacted]	[redacted]
TTD NSAI ET: Weibull (R)				
Parameter 1	[redacted]	[redacted]	[redacted]	[redacted]
Parameter 2	[redacted]	[redacted]	[redacted]	[redacted]
Hazard Ratios Applied to Base OS Curve, by Post-Progression Regimen, , ET-resistant				
Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]
Eve+Exe	[redacted]	[redacted]	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]	[redacted]	[redacted]
Anastrozole	[redacted]	[redacted]	[redacted]	[redacted]
Exemestane	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]	[redacted]	[redacted]
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
Hazard Ratios Applied to Base PFS and TTD Curve, by Post-Progression Regimen, ET-resistant				
Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]
Eve+Exe	[redacted]	[redacted]	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]	[redacted]	[redacted]
Anastrozole	[redacted]	[redacted]	[redacted]	[redacted]
Exemestane	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]	[redacted]	[redacted]
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
Hazard Ratios Applied to Base OS Curve, by Post-Progression Regimen, ET-sensitive				
Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]	[redacted]	[redacted]
Anastrozole	[redacted]	[redacted]	[redacted]	[redacted]
Exemestane	[redacted]	[redacted]	[redacted]	[redacted]

Tamoxifen	[redacted]	[redacted]	[redacted]	[redacted]
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
Hazard Ratios Applied to Base PFS and TTD Curve, by Post-Progression Regimen, ET-sensitive				
Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]	[redacted]	[redacted]
Anastrozole	[redacted]	[redacted]	[redacted]	[redacted]
Exemestane	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]	[redacted]	[redacted]
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
Adverse Event rates, RIB+ET				
Alanine aminotransferase increased	7.68 %	6.67 %	8.75 %	Beta
Neutropenia	28.11 %	26.37 %	29.88 %	Beta
Adverse Event rates, ET				
Alanine aminotransferase increased	0.70 %	0.41 %	1.06 %	Beta
Neutropenia	0.57 %	0.31 %	0.91 %	Beta
Cost per Service				
GP visit	156.00	93.64	245.83	Lognormal
Mammogram	661.00	395.78	1,039.02	Lognormal
Oncologist visit	1,578.00	944.83	2,480.45	Lognormal
ECG	287.37	172.06	451.71	Lognormal
CT scan	2,701.00	1,617.23	4,245.68	Lognormal
Mastectomy	154,495.00	92,504.46	242,849.51	Lognormal
Larger mammae operation	17,802.00	10,659.01	27,982.83	Lognormal
Lumpectomy	80,119.00	47,971.55	125,938.44	Lognormal
Radiotherapy	15,817.00	9,470.49	24,862.62	Lognormal
Patient time cost per visit	376.00	225.13	591.03	Lognormal

Transportation cost	140.40	84.07	220.69	Lognormal
PET/CT	3,737.00	2,237.54	5,874.16	Lognormal
Cost of Adverse events				
Alanine aminotransferase increased	1,957.00	1,171.76	3,076.19	Lognormal
Neutropenia	2,208.00	1,322.05	3,470.74	Lognormal
Cost of SPM progression	1,578.00	944.83	2,480.45	Lognormal
Cost of terminal care	89,879.00	53,815.39	141,280.11	Lognormal
Alanine aminotransferase increased	-0.005	-0.0026	-0.0026	Lognormal
Neutropenia	-0.007	-0.0036	-0.0104	Lognormal
Health state utilities				
Please refer to D2003:J2064 and D2068:L2080 in the health economic model				
PPS treatment costs				
Fixed, monthly cost of PPS treatments, ET-Resistant	4,127.34	2,104.95	6,149.74	Normal
Fixed, monthly cost of PPS treatments, ET-Sensitive	4,127.34	2,104.95	6,149.74	Normal

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

Not applicable efficacy and safety based solely on the NATALEE RCT.

Table 83 Bibliographic databases included in the literature search, N/A

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	N/A		
Medline			
CENTRAL			

Abbreviations:

Table 84 Other sources included in the literature search, N/A

Source name	Location/source	Search strategy	Date of search
e.g. NICE	N/A		
e.g. EMA website			

Abbreviations:

Table 85 Conference material included in the literature search, N/A

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	N/A			

H.1.1 Search strategies

Not applicable.

Table 86 of search strategy table for [name of database], N/A

No.	Query	Results
#1		

No.	Query	Results
#2		
#3		
#4		
#5		
#6		
#7		
#8		
#9		
#10		

H.1.2 Systematic selection of studies

Not applicable.

Table 87 Inclusion and exclusion criteria used for assessment of studies, N/A

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population			
Intervention			
Comparators			
Outcomes			
Study design/publication type			
Language restrictions			

Table 88 Overview of study design for studies included in the analyses, N/A

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study 1						
Study 2						

H.1.3 Excluded fulltext references

Not applicable.

H.1.4 Quality assessment

Not applicable.

H.1.5 Unpublished data

Not applicable.

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

Not applicable to this assessment. A separate literature review was not conducted to inform health-related quality-of-life data. Tables below are therefore not populated.

Table 89 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
NA	NA	NA	NA

Table 90 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NA	NA	NA	NA

Table 91 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
NA	NA	NA	NA	NA

I.1.1 Search strategies

NA

Table 92 Search strategy for [name of database]

No.	Query	Results
NA	NA	NA

I.1.2 Quality assessment and generalizability of estimates

NA

I.1.3 Unpublished data

NA

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

A systematic literature review was first conducted in 2018 to identify studies that evaluated comparators of interest as treatment for HR+/HER2- advanced breast cancer. An updated SLR was then conducted in September 2024, and reports of extended follow-up for RCTs identified in the original SLR were extracted. The ITCs of PFS and OS were then conducted using the latest data from each RCT. The purpose of the updated was to identify literature for an updated ITC that was used to inform the DR states within the health economic analysis. A separate systematic literature review of clinical studies within the HR+/HER2- early breast cancer framework was utilized to inform HRs between treatment alternatives in the eBC setting. This is available on request.

The eligibility criteria for the SLR are presented in Table 93.

Table 93 Eligibility criteria to be qualified for inclusion in the SLR

Domain	Inclusion criteria	Exclusion criteria
Population	• Adults (age: ≥18 years) with HER2-negative/HR-positive ABC/mBC who did not receive any prior systemic anticancer treatment for advanced disease – 1L[†] • Adults (age: ≥18 years) with HER2-negative/HR-positive ABC/mBC whose disease progressed after prior endocrine therapy – 2L[†]	• Population did not include adult patients with HER2-negative/HR-positive ABC or relevant outcomes were not presented separately for this patient population • Patients did not have aBC/mBC or population was mixed without aBC/mBC-specific results reported separately
Interventions	*CDK4/6 inhibitors* • Abemaciclib • Palbociclib • Ribociclib • Dalpiciclib • Lerociclib • Birociclib *Endocrine therapies* • Letrozole, anastrozole, exemestane, tamoxifen, fulvestrant, elacestrant, and camizestrant *Targeted therapies (PI3K/mTOR inhibitors)* • Alpelisib • Inavolisib • Everolimus • Capivasertib *ADCs[*]* • Sacituzumab govitecan • Datopotamab Deruxtecan • Trastuzumab deruxtecan *Chemotherapy (in line with NICE guidelines [last updated on 16 August 2017])* • Docetaxel, vinorelbine, capecitabine, anthracyclines (doxorubicin, epirubicin), gemcitabine, and paclitaxel/nab-paclitaxel	• Any other intervention not in the list
Comparators	• Any intervention of interest • Placebo	-
Outcomes	Studies investigating any of the following: • OS • PFS • Overall response • Adverse events	• No outcomes of interest

Study design	• RCTs • Systematic reviews and NMAs (eligible for inclusion at the abstract review stage, but such publications were excluded at the full-text review stage after hand-searching of their reference lists)	Any other study design, including: • Single-arm studies • Observational/cohort studies • Economic evaluations • Non-systematic or narrative reviews • Editorials, notes, comments, or letters • Case reports/case studies
Publication type	• Peer-reviewed journal articles • Congress abstracts published since 2022 to 2024 (last 3 years)	• Congress abstracts published prior to 2022
Other considerations	• Abstracts or full texts in English • Human subjects • Published in or after 2019 January 2019 to June 18, 2024 • No limits to country	• Non-English abstracts or full texts • Non-human subjects • Published prior to 2019

Abbreviations: 1L, first line; 2L, second line; aBC, advanced breast cancer; ADC, antibody-drug conjugate; CDK4/6, cyclin-dependent kinase 4 and 6; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LoT, line of therapy; mBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; RCT, randomised controlled trial.

*The SLR included only few ADCs because most are still in early development.

NICE guidelines:

• aBC: diagnosis and treatment: https://www.nice.org.uk/guidance/cg81/resources/advanced-breast-cancer-diagnosis-and-treatment-pdf-975683850181

• Managing aBC (NICE pathways): https://breastcancernow.org/sites/default/files/advanced-breast-cancer-managing-advanced-breast-cancer.pdf

†Quick overview of the patient population in the MONALEESA trials for 1L and 2L:

• Adults (≥18 years) with HER2-negative, HR-positive, aBC/mBC whose disease recurred/relapsed, with documented evidence of relapse >12 months after completing (neo)adjuvant endocrine therapy and without any prior treatment for advanced/metastatic disease

• Adults (≥18 years) with HER2-negative, HR-positive, aBC/mBC whose disease recurred/relapsed, with documented evidence of relapse >12 months after completing (neo)adjuvant endocrine therapy and with subsequent progression after one line of endocrine therapy for advanced/metastatic disease

In accordance with the early breast cancer model requirements, the SoFEA, NorBreast, and BOLERO-6 trials were included in the current SLR as no subsequent studies were published in or after 2019 (timeframe selected in the current SLR). Additionally, approximately 10 trials overlapped between the current and previous SLRs; hence, relevant data across timepoints were included in the current review.

ADCs were not included in this SLR because they did not meet all of this SLR's inclusion criteria or because of unavailability of subgroup data per LoT (1L or 2L). However, a section specific to ADCs has been included in the report due to their potential competitive advantage.

J.1.1 Biomedical database searching

A comprehensive search was performed on multiple data sources, including biomedical databases, from 2019 to current (18 June 2024). The Ovid platform databases, including MEDLINE, MEDLINE (R) In-Process, EMBASE, CDSR, DARE, and CENTRAL, were searched from 2019 to 18 June 2024.

J.1.2 Conference proceedings search

In addition to the above biomedical databases, the following conference abstracts of the last 3 years (January 2022 to July 2024) were hand searched to retrieve the latest studies that had not yet been published in journals as full-text articles:

- American Society of Clinical Oncology (ASCO)
- American Association for Cancer Research (AACR)
- European Society for Medical Oncology (ESMO)
- The San Antonio Breast Cancer Symposium (SABCS)
- European Breast Cancer Conference (EBCC)
- Advanced Breast Cancer (aBC)
- Additionally, a bibliographic search of relevant SLRs and meta-analyses was performed to retrieve relevant studies.

J.1.3 Data collection and extraction

The data collection process was in line with the Cochrane Handbook for Systematic Reviews of Interventions [39] and PRISMA guidelines [38]. The collection of data involved two steps: (1) screening based on title and abstract, and (2) detailed screening based on full text.

After the retrieval of citations through the literature search, the citations were initially screened for inclusion based on their titles and abstracts. Each citation was screened by two independent reviewers, and any discrepancies between the reviewers were reconciled by a third independent reviewer. Studies that qualified through the first stage of screening underwent a second stage of screening based on the full-text publications. Full-text publications were screened using more specific eligibility criteria. Each full-text publication was also screened by two independent reviewers, and any discrepancies between the reviewers were reconciled by a third independent reviewer.

Data from the included studies were extracted into a predefined extraction grid. The data extraction process was carried out by two independent reviewers, and any discrepancies were resolved by a third independent reviewer.

J.1.4 Search strategy

Table 94 Summary of search hits retrieved from the Ovid® database [2019 to current (18 June 2024)]

No.	Query	Results
1	exp breast neoplasms/ or exp breast cancer/	984764
2	(breast$ adj3 (cancer$ or neoplas$ or oncolog$ or tumo?r$ or malignanc$ or carcinoma$ or adenocarcinoma$ or sarcoma$)).ti,ab.	1005757
3	(mammar$ adj3 (cancer$ or neoplas$ or oncolog$ or tumo?r$ or malignanc$ or carcinoma$ or adenocarcinoma$ or sarcoma$)).ti,ab.	58056
4	(metasta$ or advance$ or second$ or recurren$ or inoperab$ or disseminat$ or incur$).ti,ab,sh.	10639909
5	(1 or 2 or 3) and 4	468047
6	exp Breast/ and exp Neoplasm Metastasis/	17118
7	(breast$ adj3 (metasta$ or advance$ or second$ or recurren$ or inoperab$ or disseminat$ or incur$)).ti,ab.	162481
8	(mammar$ adj3 (metasta$ or advance$ or second$ or recurren$ or inoperab$ or disseminat$ or incur$)).ti,ab.	4444
9	(breast$ or mammar$).ti,ab,sh.	1657261
10	((stage or grade or type) adj2 ("3" or III or "c" or "4" or "IV" or d)).ti,ab.	964334
11	(N1 or N2$ or N3$ or pN1$ or pN2$ or pN3$).ti,ab,sh.	895734
12	9 and (10 or 11)	83274
13	5 or 6 or 7 or 8 or 12	514147
14	(letrozole or Femara or CGS 20267 or CGS-20267 or 112809-51-5).ti,ab,rn,kw.	24361
15	(anastrozole or Arimidex or ZD1033 or ZD-1033 or ICI D1033 or 120511-73-1).ti,ab,rn,kw.	15899
16	(exemestane or examestane or Aromasin or Aromasine or Aromasil or FCE 24304 or FCE-24304 or 107868-30-4).ti,ab,rn,kw.	10734

17	(Tamoxifen or Nolvadex or Novaldex or Soltamox or Tomaxithen or Zitazonium or ICI 46474 or ICI-46474 or ICI 47699 or ICI-47699 or 10540-29-1).ti,ab,rn,kw.	109857
18	(fulvestrant or Faslodex or ICI 182780 or ICI-182780 or ZM 182780 or ZM-182780 or 129453-61-8).ti,ab,rn,kw.	18057
19	(elacestrant or 'er 306323' or er306323 or korserdu or orserdu or 'ela 0121' or ela0121 or 'rad 1901' or rad1901).ti,ab,rn,kw.	349
20	(camizestrant or 'az 14066724' or az14066724 or 'azd 9833' or azd9833 or azd-9833).ti,ab,rn,kw.	121
21	(everolimus or Afinitor or Certican or RAD001 or "RAD 001" or SDZ RAD or SDZ-RAD or 159351-69-6).ti,ab,rn,kw.	50015
22	(palbociclib or Ibrance or "PD 0332991" or PD-0332991 or 571190-30-2).ti,ab,rn,kw.	10791
23	(LEE011 or LEE-011 or Ribociclib or 1211441-98-3).ti,ab,rn,kw.	4643
24	(abemaciclib or LY2835219 or LY2835210 or 1231929-97-7).ti,ab,rn,kw.	4979
25	(dalpiciclib or C000720752 or 5ZHA5P4PFX).ti,ab,rn,kw.	136
26	(lerociclib or 'g1t 38' or g1t38 or GB491).ti,ab,rn,kw.	53
27	(docetaxel or Taxotere or Docefrez or RP 56976 or RP-56976 or 114977-28-5).ti,ab,rn,kw.	108336
28	(Vinorelbine$ or noranhydrovinblastine$ or anhydrovinblastine$ or "anx 530" or anx530 or eunades$ or exelbine$ or "kw 2307" or kw2307 or navelbin$ or navirel$ or vinbine$ or vinelbine$).ti,ab,rn,kw.	27104
29	(capecitabine or Xeloda or 154361-50-9).ti,ab,rn,kw.	55205
30	(doxorubicin or Adriamycin or Doxil or Adriablastin or Adriablastine or Adriblastin or Adriblastina or Adriblastine or Adrimedac or Doxolem or Doxorubicin or Doxotec or Farmiblastina or Myocet or Onkodox or Ribodoxo or Rubex 23214-92-8).ti,ab,rn,kw.	314430
31	(Epirubicin$ or epiadriamycin$ or epidoxo$ or epirubicin$ or binarin$ or ellence$ or epidx$ or epifil$ or epilem$ or farmorrubicina$ or farmorubicin$ or pharmarubicin$ or "imi 28" or "nsc 256942" or pidorubicin$).ti,ab,rn,kw.	44927
32	(Gemcitabine$ or difluorocytidine$ or difluorodeoxycytidine$ or Gemcite$ or Gemzar$ or "ly 188011" or ly188011).ti,ab,rn,kw.	108457

33	('nab paclitaxel' or nab-paclitaxel or 'abi-007' or paclitaxel or abraxane or NSC-125973 or NSC125973 or Anzatax or Onxol or Praxel or Taxol or 'bms 181339' or bms181339 or 'bmy 45622' or bmy45622 or paxital).ti,ab,rn,kw.	206652
34	(alpelisib or piqray or vijoice or BYL719 or BYL-719).ti,ab,rn,kw.	3264
35	(inavolisib or ro7113755 or "ro 7113755" or "gdc 0077" or gdc0077 or "rg 6114" or rg6114).ti,ab,rn,kw.	112
36	(capivasertib or 'azd 5363' or azd-5363 or azd5363 or truqap).ti,ab,rn,kw.	1160
37	(''isactuzumab govitecan'' or ''sacituzumab govitecan hziy'' or ''sacituzumab govitecan-hziy'' or trodelvy or ''sacituzumab govitecan'').ti,ab,rn,kw.	1868
38	('datopotamab deruxtecan' or 'dato-dxd' or 'ds 1062' or 'ds 1062a' or ds1062 or ds1062a).ti,ab,rn,kw.	293
39	('trastuzumab deruxtecan' or 'ds 8201' or 'ds 8201a' or ds8201 or ds8201a or enhertu or 'fam trastuzumab deruxtecan nxki' or 'fam-trastuzumab deruxtecan-nxki').ti,ab,rn,kw.	3087
40	(birociclib or 'XZP 3287' or XZP-3287 or XZP3287).ti,ab,rn,kw.	7
41	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40	835040
42	randomized controlled trial.pt,sh.	1348651
43	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.	5101379
44	(retraction of publication or retracted publication).pt.	47915
45	42 or 43 or 44	5326099
46	(animals not humans).sh.	3017349
47	((comment or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence) not "randomized controlled trial").pt.	10179802
48	(random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not "randomized controlled trial".pt.	321478
49	45 not (46 or 47 or 48)	4485905
50	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.	5101379
51	RETRACTED ARTICLE/	14888

52	50 or 51	5115711
53	(animal$ not human$).sh,hw.	7979644
54	(book or conference paper or editorial or letter or review).pt.	10525019
55	(random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab.	324084
56	exp randomized controlled trial/	1352357
57	54 or 55	10790346
58	57 not 56	10729109
59	52 not (53 or 58)	4150142
60	49 or 59	4565645
61	13 and 41 and 60	22793
62	exp Animal/	50894809
63	(rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,sh.	12437537
64	nonhuman/	7759536
65	62 or 63 or 64	53652942
66	exp Human/ or Human Experiment/	42608162
67	65 not 66	11046175
68	(letter or note or editorial or comment or addresses or bibliography or book or "book series" or chapter or "legal cases").pt.	5086805
69	61 not (67 or 68)	22495

70	limit 69 to yr="2019 -Current"	7018
71	limit 70 to english language	6981
72	limit 71 to humans	6759
73	limit 72 to yr="2019 - 2022"	4972
74	limit 72 to yr="2023 -Current"	1797
75	remove duplicates from 73	3409
76	remove duplicates from 74	1324
77	**75 or 76**	**4750**

Table 95 Search terms for congress websites in the overall SLR

Conference	Year	Abstract search links	Search terms	Date accessed	Search methodology	No. of hits	No. of references included
American Society of Clinical Oncology (ASCO) Annual Meeting	2022	https://meetings.asco.org/abstracts-presentations/search	HR+ HER2- breast cancer, HER2 negative breast cancer, advanced breast cancer	17.06.2023	Used year (2022) filter Used ASCO annual meeting filter	175	1
	2023	https://meetings.asco.org/abstracts-presentations/search		14.06.2024	Used year (2023) filter Used ASCO annual meeting filter	220	1
	2024	https://meetings.asco.org/abstracts-presentations/search		14.06.2024	Used year (2024) filter Used ASCO annual meeting filter	225	4
European Society for Medical Oncolog	2022	https://www.annalsofoncology.org/issue/S0923-7534(22)X0014-8	Breast cancer	04.07.2024	By screening all the studies available online	-	0
	2023	https://www.annalsofoncology.org/iss		04.07.2024	By screening all the	-	0

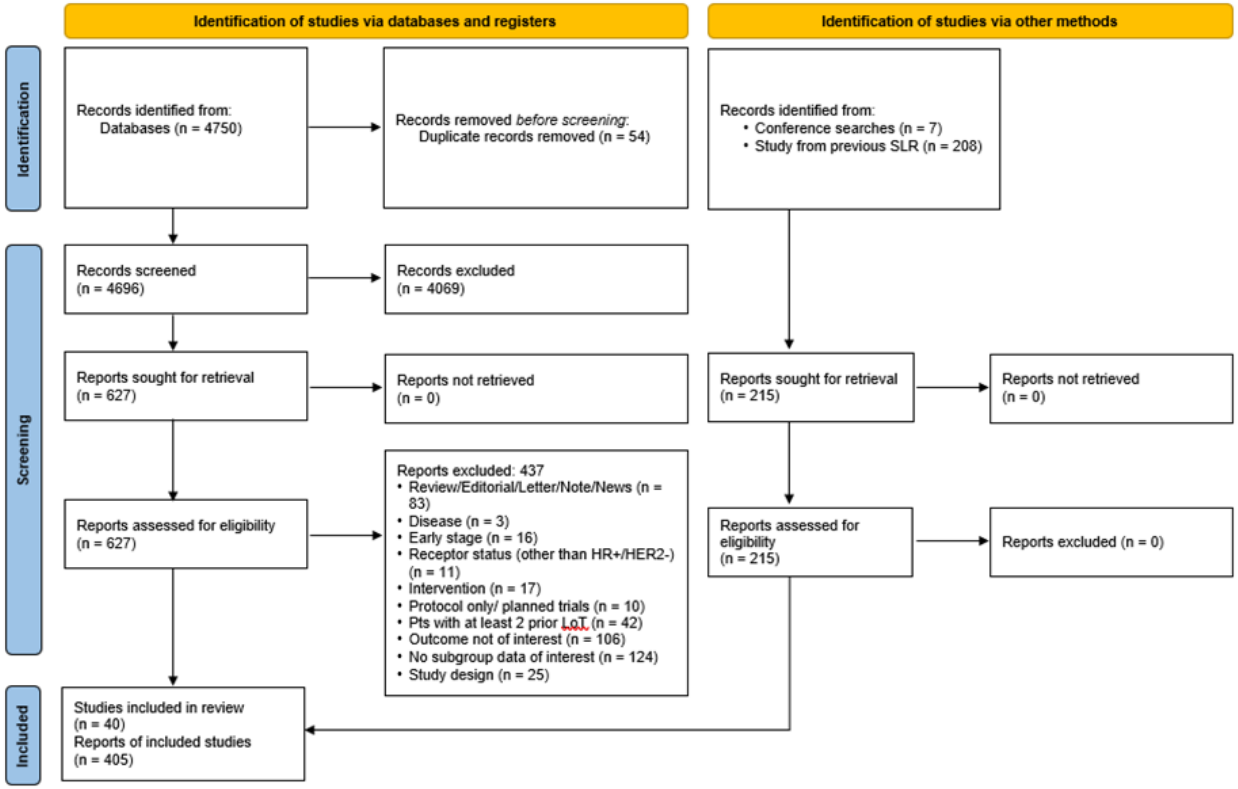
y (ESMO) Congress		ue/S0923-7534(23)X0011-8			studies available online		
	2024	https://www.annalsofoncology.org/issue/S0923-7534(24)X0010-1		04.07.2024	By screening all the studies available online	-	0
ESMO breast	2022	https://oncologypro.esmo.org/meeting-resources/esmo-breast-cancer-congress-2022?event_resources_filter_form%5Bformat%5D%5B%5D=abstract&event_resources_filter_form%5Bformat%5D%5B%5D=ePoster&event_resources_filter_form%5Bsearch%5D=Breast%20cancer	Breast cancer	04.07.2024	By screening all the studies available online	-	0
	2023	https://oncologypro.esmo.org/meeting-resources/esmo-breast-cancer-congress?event_resources_filter_form%5Bformat%5D%5B%5D=abstract&event_resources_filter_form%5Bformat%5D%5B%5D=ePoster&event_resources_filter_form%5Bsearch%5D=		04.07.2024	By screening all the studies available online	413	0
	2024	https://oncologypro.esmo.org/meeting-resources/esmo-breast-cancer-2024?event_resources_filter_form%5Bsearch%5D=breast%20cancer		04.07.2024	By screening all the studies available online	420	0
American Association of Cancer Research (AACR)	2022	https://aacrjournals.org/cancerres/search-results?q=breast+cancer&fl_SiteID=100011&rg_PublicationDate=06%2f15%2f2022+TO+06%2f	Breast cancer	16.07.2024	By screening all the studies available online	-	0

		15%2f2022&page=1&f_ArticleTypeDisplayName=Abstract					
	2023	https://aacrjournals.org/cancerres/search-results?q=breast+cancer&fl_SiteID=1000011&rg_PublicationDate=04%2f01%2f2023+TO+04%2f15%2f2023&page=1&f_ArticleTypeDisplayName=Abstract	Breast cancer	16.07.2024	By screening all the studies available online	-	0
	2024	Abstract book	Breast cancer	04.07.2024	Searched entire abstract book	6200	0
St. Antonio Breast Cancer Symposium (SABCS)	2022	Abstract book	Advanced breast cancer, Metastatic breast cancer	22.07.2024	Searched entire abstract book	826	0
	2023	Abstract book		19.07.2024	Searched entire abstract book	891	0
	2024	Abstract book		19.07.2024	Searched entire abstract book	800	1
European Breast Cancer Conference (EBCC)	2022	Abstract book	Breast cancer	24.06.2024	Searched entire abstract book	969	0
	2024	Abstract book		24.06.2024	Searched entire abstract book	1061	0
Advanced breast cancer (aBC)	2023	https://www.sciencedirect.com/journal/the-breast/vol/71/suppl/S1	Breast cancer	24.06.2024	By screening all the studies available online	224	0

J.1.5 PRISMA flow and search results

A PRISMA flow diagram illustrating the study selection process is presented in Figure 5. A total of 4750 records were identified from the medical database searches conducted on 18 June 2024. Owing to the overlap in coverage between the databases, 54 abstracts were found to be duplicates. Following the title and abstract screening of the 4696 citations, 627 potentially relevant references were identified. Full-text reports of these 627 references were obtained for a more detailed evaluation, of which 437 references were excluded based on predefined criteria in the protocol. Additionally, 215 studies were included from other sources, comprising seven from conference searches and 208 from the previous SLR. Overall, 40 studies from 405 publications were selected for data extraction. Of these only 8 was eventually used in the Danish submission for an ITC to model the DR-states.

Figure 47 Flow of evidence through the SLR (PRISMA diagram)



HER2: Human epidermal growth factor receptor 2; HR: Hormone receptor; LoT: Line of therapy; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR: Systematic literature review.

In accordance with the early breast cancer (eBC) model requirements, the SoFEA, NorBreast, and BOLERO-6 trials were included as no subsequent studies were published in or after 2019 (timeframe selected in the current SLR).

Thus, these three trials were incorporated into the current SLR. Additionally, approximately 10 trials overlapped between the current and previous SLRs; hence, relevant data across timepoints were included in the current review.

Table 96 A list of the 40 trials included in the global SLR and, which are used in the local submission

Trial name*	Author year	Trial registry ID	Design	LoT	Population	Intervention	Comparator	Included in submission
CDK4/6 inhibitors								
MONALEESA-2 (60)	Hortobagyi 2022	NCT01958021	Phase III, double-blind	1L	Post-menopausal women with HR+/HER2- aBC	Ribociclib + Letrozole	Placebo + Letrozole	Yes
MONALEESA-3 (50)	Neven 2023	NCT02422615	Phase III, double-blind	1L and 2L	Post-menopausal women with HR+/HER2- aBC	Ribociclib + Fulvestrant	Placebo + Fulvestrant	Yes
MONALEESA-7	Lu 2022	NCT02278120	Phase III, double-blind	1L	Pre-menopausal women with HR+/HER2- aBC	Ribociclib + Endocrine therapy	Placebo + Endocrine therapy	No
PALOMA-1/TRIO-18	Finn 2020	NCT00721409	Phase II, open label	1L	Post-menopausal women with ER+/HER2- aBC	Palbociclib + letrozole	Letrozole	No
PALOMA-2	Slamon 2024	NCT01740427	Phase III, double-blind	1L	Post-menopausal women with ER+/HER2- aBC	Palbociclib + Letrozole	Placebo + Letrozole	No
PALOMA-3 (53)	Cristofanilli 2022	NCT01942135	Phase III, double-blind	1L and 2L	Pre- and post-menopausal women with HR+/HER2- aBC	Palbociclib + Fulvestrant	Placebo + Fulvestrant	No
PALOMA-4	Xu 2022	NCT02297438	Phase III, double-blind	1L	Post-menopausal women with ER+/HER2- aBC	Palbociclib + Letrozole	Placebo + Letrozole	No
MONARCH-2 (55, 56)	Grischke 2023	NCT02107703	Phase III, double-blind	1L and 2L	Pre- and post-menopausal women with HR+/ERBB2- aBC	Abemaciclib + Fulvestrant	Placebo + Fulvestrant	Yes
MONARCH-3 (63)	Goetz 2024	NCT02246621	Phase III, double-blind	1L	Post-menopausal women with HR+/HER2- aBC	Abemaciclib + Anastrozole or letrozole	Placebo + Anastrozole or letrozole	Yes

DAWNA-2	Zhang 2023	NCT03966898	Phase III, double-blind	1L	Pre- and post-menopausal women with HR+/HER2- aBC	Dalpiciclib + Anastrozole or letrozole	Placebo + Anastrozole or letrozole	No
KENDO	Schettini 2024	NCT03227328	Phase II, open label	1L	Pre- and post-menopausal women with HR+/HER2- aBC	CDK4/6 Inhibitor (Palbociclib, ribociclib, abemaciclib) + Endocrine therapy (aromatase inhibitor, fulvestrant)	Chemotherapy (Anthracycline-based, taxane-based, capecitabine monotherapy, capecitabine + vinorelbine) ± endocrine therapy (aromatase inhibitor, fulvestrant)	No
NR	Hamed 2024	NCT05670054	Phase III, open label	2L	Pre- and post-menopausal women with ER+ or PR+/HER2- aBC	Palbociclib + Fulvestrant	Ribociclib + Fulvestrant	No
LEONARDA-2	Hu 2024	NCT05851014	Phase III, double-blind	1L	Pre- or peri-menopausal and post-menopausal women with HR+/HER2- aBC	Lerociclib + Letrozole	Placebo + Letrozole	No
PALMIRA	Antonio 2023	NCT03809988	Phase II, open label	2L	Pre- and post-menopausal women with HR+/HER2- aBC	Palbociclib + endocrine therapy (letrozole or fulvestrant)	Endocrine therapy (letrozole or fulvestrant)	No
AMALEE	Cardoso 2023	NCT03822468	Phase II, open label	1L	Pre- and post-menopausal women with HR+/HER2- aBC	Ribociclib 400 mg + NSAI + goserelin in pre-menopausal women	Ribociclib 600 mg + NSAI + goserelin in pre-menopausal women	No
GEICAM/2014-12 (FLIPPER)	Albanell 2022	NCT02690480	Phase II, double-blind	1L	Post-menopausal women with HR+/HER2- aBC	Palbociclib + fulvestrant	Placebo + fulvestrant	No

RIGHT Choice (68)	Lu 2024	NCT03839823	Phase II, open label	1L	Pre-menopausal women with ER+ or PR+/HER2- aBC	Ribociclib + letrozole or anastrozole, goserelin	Investigator's choice of combination chemotherapy*	Yes
MONARCH plus (cohort A & B)	Zhang 2020 (cohort A)	NCT02763566	Phase III, double-blind	1L and 2L	Post-menopausal women with HR+/HER2- aBC	Abemaciclib +NSAI	Placebo + NSAI	No
	Zhang 2020 (cohort B)	NCT02763566	Phase III, double-blind	1L and 2L	Post-menopausal women with HR+/HER2- aBC	Abemaciclib + fulvestrant	Placebo + fulvestrant	No
Targeted therapy								
SOLAR-1	André 2021	NCT02437318	Phase III, double-blind	1L and 2L	Post-menopausal women with ER+ or PR+/HER2- aBC	Alpelisib + fulvestrant	Placebo + fulvestrant	No
MAIN-A (MAINtenance Afinitor)	Guarneri 2021	EudraCT: 2013-004153-24	Phase III, open label	1L - MAIN	Post-menopausal women with HR+/HER2- aBC	Everolimus + letrozole or anastrozole or exemestane (aromatase inhibitors)	Letrozole or anastrozole (aromatase inhibitors)	No
BOLERO-2 (59)	Beck 2014	NCT00863655	Phase III, double-blind	1L	Post-menopausal women with ER+/HER2- aBC	Everolimus + exemestane	Placebo + exemestane	Yes
BOLERO-6	Jerusalem 2018	NCT01783444	Phase II, open label	2L	Post-menopausal women with ER+/HER2- aBC	Everolimus + exemestane	Everolimus, or capecitabine	No
MIRACLE	Fan 2021	NCT02313051	Phase II, open label	1L	Pre-menopausal women with HR+/ERBB2- aBC	Everolimus + letrozole + goserelin	Letrozole + goserelin	No
The LEO study	Jeong 2021	NCT02344550	Phase II, open label	1L and 2L	Pre-menopausal women with HR+/HER2- aBC	Everolimus + letrozole + leuprorelin	Letrozole + leuprorelin	No
INAVO120	Kummel 2024	NCT04191499	Phase III, double-blind	1L	Pre- and post-menopausal women with HR+/HER2- aBC	Inavolisib + palbociclib + fulvestrant	Placebo + palbociclib + fulvestrant	No
Endocrine therapy								

PADA-1	Hardy-Bessard 2022	NCT03079011	Phase III, open label	1L	Pre- and post-menopausal women with ER+/HER2- aBC	Aromatase inhibitor + palbociclib	Fulvestrant + palbociclib	No
Chloe	Shien 2023	jRCTs061180075	Phase II, open label	1L	Post-menopausal women with ER+/HER2- aBC	Aromatase inhibitor + everolimus	Aromatase inhibitor	No
SONIA	Sonke 2023	NCT03425838	Phase III, open label	1L	Pre- and post-menopausal women with HR+/HER2- aBC	NSAI (either letrozole or anastrozole) + CDK4/6 inhibitors (palbociclib, ribociclib, or abemaciclib depending on availability and physician's preference)	NSAI only (either letrozole or anastrozole)	No
OVERSTEP	Huang 2022	NCT02597868	Phase not reported, open label	1L - MAIN	Patients with HR+/HER2- aBC	Endocrine therapy	Capecitabine alone	No
SoFEA (58)	Johnston 2013	NCT00253422	Phase III, double-blind	2L	Post-menopausal women with HR+/HER2- aBC	Fulvestrant + anastrozole	Fulvestrant + placebo; Exemestane	Yes
PARSIFAL	Llombart-Cussac 2024	NCT02491983	Phase II, open label	1L	Pre- and post-menopausal women with HR+/ERBB2- aBC	Fulvestrant + palbociclib	Letrozole + palbociclib	No
FALCON (64)	Robertson 2023	NCT01602380	Phase III, double-blind	1L	Post-menopausal women with ER+ or PR+/HER2- aBC	Fulvestrant	Anastrozole	Yes
SWOG S1222	Moore 2021	NCT021378737	Phase III, open label	1L	Post-menopausal women with HR+/HER2- aBC	Fulvestrant	Fulvestrant + everolimus; Fulvestrant + everolimus + anastrozole	No

SWOG S0226	Mehta 2019	NCT00075764	Phase III, open label	1L	Post-menopausal women with HR+/HER2- aBC	Anastrozole	Anastrozole + fulvestrant	No
FRIEND	Wang 2023	NCT02646735	Phase II, open label	1L	Post-menopausal women with ER+/HER2- aBC	Exemestane 25 mg	Fulvestrant 500 mg	No
MD-127-2019	Azim 2024	NCT04571437	Phase II, open label	1L	Pre- and post-menopausal women with ER+/HER2- aBC	Letrozole + capecitabine	Letrozole	No
Chemotherapy								
EFFECT	Biganzoli 2020	NCT02783222	Phase II, open label	1L	Pre- and post-menopausal with HR+/HER2- aBC	Nab-paclitaxel 100 mg	Nab-paclitaxel 125 mg	No
NorBreast-231	Aapro 2019	NR	Phase II, open label	1L	Patients with HR+/HER2- aBC	Vinorelbine	Paclitaxel	No
NR	Liu 2023	NCT04192331	Phase II, open label	1L and 2L	Patients with HR+/HER2- mBC	Nab-paclitaxel (3 weeks)	Nab-Paclitaxel (4 weeks)	No
VicTORia	Decker 2019	NCT01520103	Phase II, open label	2L	Pre- and post-menopausal women with HR+/HER2- aBC	Vinorelbine + everolimus	Vinorelbine	No

*only trials used for the Danish dossier is provided with full reference (see section 15).

Appendix K. DBCG registry data

Due to ongoing efforts to publish this data the results are considered confidential as per request and agreement with the DBCG (data owner). In the following, information regarding the DBCG registry data is provided as a background to understand the data presented in this dossier. The full registry study included additional analyses and cohorts, which were not used here, as they are not relevant to the dossier, and will not be described in the following.

Data handling and method

Purpose

To report on data from the clinical database of DBCG for patients with HR+ HER2- eBC in scope for adjuvant ribociclib treatment as per the full indication.

Design

A non-interventional, observational, retrospective cohort study including patients registered to the DBCG database.

Data collection

The DBCG was established in 1977 and has since then provided guidelines for treatment of breast cancer patients, conducted nationwide clinical trials of adjuvant breast cancer therapy, and collected data into the database.

From Danish hospital departments of surgery, pathology, and oncology, breast cancer patients are reported prospectively to the database of the DBCG with information on date and type of surgery and on prognostic factors allowing allocation to the treatment protocols, and with detailed information on adjuvant treatment.

The patients are followed by the hospital to a total of 10 years of follow up. Date, location of recurrences, and end of follow up without recurrence at 10 years is reported to the DBCG. Patients may be withdrawn earlier than 10 years after surgery by one of the following reasons: Patient want to stop, recurrence of the disease, any other malignant disease, lost to follow up, or death.

Chemotherapy is recorded with specific dose and date for each agent administered. ET is recorded with type of agent every 6 months.

For a complete follow-up on vital status data were linked with the Danish Civil Registration System.

Population

Two cohorts are considered and includes patients with their first invasive breast cancer.

Cohort 1; Patients diagnosed 2014-2019 and Cohort 2; Patients diagnosed 2020-2022. Both cohorts include patients with HR+ HER2- eBC and fulfilling one of the following criteria in order to approximate the NATALEE inclusion criteria:

- T3-T4
- N2-N3
- (T2: N1 or grade III)
- (T1: N1mac)
- T1: N1mic and grade III)

N0 patients are included if the fulfil T3-T4 or T2&GradeIII.

ER- and HER2-status by surgical specimen at up-front surgery or biopsy. For patients with up-front surgery, tumor size is determined by surgical specimen and lymph node status by sentinel node procedure and/or axillary dissection. For patients with pre-operative systemic therapy tumor size is determined by ultrasound measurement and nodal status primarily on FNA axilla, with a minor part having up-front SN information.

DBCG cohort vs. NATALEE trial (included and excluded subgroups)

DBCG selected the patients based on the NATALEE inclusion criteria, which would constitute an approximation of the NATALEE population in Danish clinical practice. As seen from table below very minor differences are noted between the included population.

Table 97 DBCG – DBCG cohort vs. NATALEE trial (included and excluded subgroups)

T	N	Grade	Stage	NATALEE	DBCG cohort 1a
T0	N1mi	-	1b		
	N1ma		2a		
T1	N0	I-II	1a		
	N1mi	I-II	1b		
		III	1b		
	N1ma	I-II	2a		
		III	2a		
T2	N0*	I-II	2a		
		III	2a		
	N1	I-II	2b		
		III	2b		
T3	N0*	-	2b		
	N1	-	3a		
Any	N2	-	3b		
	N3	-	3b		
T4	N0	-	3b		
	N1-2	-			

The results in this report are from cohort 1a. Patients in cohort 1a was diagnosed with with their first invasive breast cancer in 2014-2019 and only included patients who received ET. Cohort 1a was chosen because their treatment aligns with current standards, and they had sufficient follow-up time for a meaningful outcome analysis (7-year landmark). Due to the nature of the disease, the cohort from 2020-2022 was deemed to have too short follow-up to provide meaningful prognostic information about the population. Further an additional subgroup analysis of cohort 1a based on nodal status is reported.

Efficacy data will include three outcomes:

Invasive Disease-Free Survival (iDFS) is defined as the time from date of diagnosis to date of first event of ipsilateral invasive breast cancer recurrence, regional invasive breast cancer recurrence, distant recurrence, death attributable to any cause, contralateral invasive breast cancer, or second non-breast invasive cancer.

Distant Disease-Free Survival (DDFS) is defined as the time from date of diagnosis to date of first event of distant recurrence, death (any cause), or second primary non-breast invasive cancer. Loco-regional recurrence alone and contralateral BC as first events will be handled as competing events.

Distant Disease-Free Survival (DRFS) is defined as the time from date of diagnosis to date of first event of distant recurrence, death (any cause). Second primary non-breast invasive cancer, Loco-regional recurrence alone and contralateral BC as first events will be handled as competing events.

Overall survival (OS) is defined at time from date of diagnosis to the date of death of any cause.

Incidence rates on cohort 1 and cohort 2 are reported for each cohort in total (data used in the incident and eligible patient estimation).

Patient characteristics of cohort 1 including age, menopausal status, nodal status, histological type and grade, type of ET and chemotherapy (neo- vs adjuvant vs no) will be presented. Grade is recorded for patients with ductal or lobular carcinoma.

For cohort cohort 1a; iDFS, DDFS and OS will be calculated.

For iDFS cohort 1a subgroups analysis is also presented for nodal status (N0, N1,N2-3)

Statistical analysis

The DBCG undertook central review, query, and analysis of data. Follow-up time is quantified in terms of a Kaplan-Meier estimate of potential follow-up. The Kaplan-Meier method was used to estimate IDFS, OS and adherence to ET. DDFS is estimated by cumulative incidence in the presence of competing risk.

[redacted]. A minor part of the patients is allocated outside a protocolled treatment program with follow-up data not retrieved

systematically, and the primary cause being previous or simultaneous non-breast invasive cancer.

- Discontinuation of ET for patients in cohort 1a is calculated from date of first ET until:
- End-of-ET by a registration of no-ET or date-of-ET-stop following last recorded ET and within 4½ years (discontinuation)
- Off-study within 6 months of last recorded ET (censored)
- End-of-ET by a registration of no-ET or date-of-ET-stop following last recorded ET ≥4½ years (censored)
- Last date of ET (censored); including patients with ET ≥4½ years, patients diagnosed and started ET within 4½ years or patients with partly missing information on ET (eg last recording in 2022)

Data analyses was performed using SAS EG 8.3.3.181.

Baseline and Treatment characteristics

The cohort had a median age (IQR) of 62 (51; 73).

Table 98 Baseline Characteristics

DBCG cohort (NATALEE criteria)		
Characteristics	N	%
Age group		
<50 years of age	[redacted]	[redacted]
50-59 Years	[redacted]	[redacted]
60-69 Years	[redacted]	[redacted]
70-79 Years	[redacted]	[redacted]
≥ 80 Years	[redacted]	[redacted]
Menopausal status		
Premenopausal	[redacted]	[redacted]
Postmenopausal	[redacted]	[redacted]
Nodal status		
N0	[redacted]	[redacted]
N1	[redacted]	[redacted]
N2	[redacted]	[redacted]
N3	[redacted]	[redacted]
Tumor size		
T1	[redacted]	[redacted]
T2	[redacted]	[redacted]
T3	[redacted]	[redacted]
T4	[redacted]	[redacted]
Histological type		
Ductal	[redacted]	[redacted]
Lobular	[redacted]	[redacted]

Other	[redacted]	[redacted]
Malignancy grade		
Malignant, NOS	[redacted]	[redacted]
Grade I	[redacted]	[redacted]
Grade II	[redacted]	[redacted]
Grade III	[redacted]	[redacted]
Unknown	[redacted]	[redacted]

Table 99 Treatment Characteristics

DBCG-cohort (NATALEE criteria)		
Characteristics	N	%
Chemotherapy		
Yes	[redacted]	[redacted]
NACT	[redacted]	[redacted]
Adjuvant	[redacted]	[redacted]
No	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Endocrine therapy		
No	[redacted]	[redacted]
Yes	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
TAM	[redacted]	[redacted]
AI	[redacted]	[redacted]
Sequential *	[redacted]	[redacted]

[redacted]

Registry data – Outcome data (iDFS, OS, DDFS, DRFS)

Figure 48 iDFS rates in the DBCG population

Figure 49 OS rates in the DBCG population

Figure 50 Cumulative DDFS incidence rate in the DBCG population

[redacted].

[redacted].

Figure 51 Type of site of events (number) and the cumulative incidence (%) at 5 years for specific events by age below or above 70 years (< or ≥ 70)

[redacted].

[redacted].

Figure 52 iDFS rates based on nodal status

[redacted]

Table 100 Registry data on 7-year iDFS, DDFS, DRFS and OS rates in the Danish ER+/HER2- population corresponding to the NATALEE population.

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Appendix L. Supplemental Clinical information

L.1 Detailed Baseline Characteristics

Table 101 Baseline demographic characteristics of patients in studies included for the comparative analysis of efficacy and safety

Baseline demographic characteristics	RIB + ET N=2,549, n (%)	ET only N=2,552, n (%)	Total N=5,101, n (%)
Age (years)			
Mean (SD)	52.9 (10.75)	52.7 (10.77)	52.8 (10.76)
Median (min–max)	52.0 (24–90)	52.0 (24–89)	52.0 (24–90)
Gender			
Male	11 (0.4)	9 (0.4)	20 (0.4)
Female	2,538 (99.6)	2,543 (99.6)	5,081 (99.6)
Menopausal status			
Premenopausal women and men	1,125 (44.1)	1,128 (44.2)	2,253 (44.2)
Postmenopausal women	1,424 (55.9)	1,424 (55.8)	2,848 (55.8)
Race			
White	1,876 (73.6)	1,868 (73.2)	3,744 (73.4)
Black or African American	42 (1.6)	47 (1.8)	89 (1.7)
Asian	341 (13.4)	334 (13.1)	675 (13.2)
Native Hawaiian or Other Pacific Islander	3 (0.1)	1 (0.0)	4 (0.1)
American Indian or Alaska Native	4 (0.2)	3 (0.1)	7 (0.1)
Other	145 (5.7)	172 (6.7)	317 (6.2)
Missing	138 (5.4)	127 (5.0)	265 (5.2)
Region			
Asia	281 (11.0)	290 (11.4)	571 (11.2)
Europe	1,505 (59.0)	1,506 (59.0)	3,011 (59.0)
North America/Australia	624 (24.5)	612 (24.0)	1,236 (24.2)
Latin America	139 (5.5)	144 (5.6)	283 (5.5)

Table 102 Baseline disease characteristics of patients in studies included for the comparative analysis of efficacy and safety

Baseline disease characteristics	RIB + ET N=2,549, n (%)	ET only N=2,552, n (%)	Total N=5,101, n (%)
ECOG performance status			
0	2,106 (82.6)	2,132 (83.5)	4,238 (83.1)
1	440 (17.3)	418 (16.4)	858 (16.8)
Missing	3 (0.1)	2 (0.1)	5 (0.1)
Histopathological grade at diagnosis			
GX	30 (1.2)	32 (1.3)	62 (1.2)
G1	218 (8.6)	240 (9.4)	458 (9.0)
G2	1,458 (57.2)	1,451 (56.9)	2,909 (57.0)
G3	521 (20.4)	549 (21.5)	1,070 (21.0)
Not done	292 (11.5)	258 (10.1)	550 (10.8)
Missing	30 (1.2)	22 (0.9)	52 (1.0)
T stage at diagnosis			
TX	175 (6.9)	173 (6.8)	348 (6.8)
T0	4 (0.2)	7 (0.3)	11 (0.2)
Tis	2 (0.1)	3 (0.1)	5 (0.1)
T1	471 (18.5)	442 (17.3)	913 (17.9)
T2	1,181 (46.3)	1,235 (48.4)	2,416 (47.4)
T3	471 (18.5)	472 (18.5)	943 (18.5)
T4	200 (7.8)	184 (7.2)	384 (7.5)
Missing	45 (1.8)	36 (1.4)	81 (1.6)
N stage at diagnosis			
NX	272 (10.7)	264 (10.3)	536 (10.5)
N0	694 (27.2)	737 (28.9)	1,431 (28.1)
N1	1,050 (41.2)	1,049 (41.1)	2,099 (41.1)
N2	332 (13.0)	292 (11.4)	624 (12.2)
N3	151 (5.9)	175 (6.9)	326 (6.4)
Missing	50 (2.0)	35 (1.4)	85 (1.7)
Predominant histology			
Invasive ductal carcinoma not specified	1,857 (72.9)	1,881 (73.7)	3,738 (73.3)
Invasive lobular	455 (17.9)	450 (17.6)	905 (17.7)
Carcinoma medullary	1 (0.0)	1 (0.0)	2 (0.0)

Baseline disease characteristics	RIB + ET N=2,549, n (%)	ET only N=2,552, n (%)	Total N=5,101, n (%)
Mucinous	17 (0.7)	16 (0.6)	33 (0.6)
Papillary	18 (0.7)	12 (0.5)	30 (0.6)
Tubular	5 (0.2)	3 (0.1)	8 (0.2)
Ductal carcinoma in situ	1 (0.0)	0	1 (0.0)
Other	194 (7.6)	189 (7.4)	383 (7.5)
Missing	1 (0.0)	0	1 (0.0)
HER2 ISH result prior to surgery (reported only if performed)			
Amplification	4 (0.2)	7 (0.3)	11 (0.2)
Non-amplification	612 (24.0)	653 (25.6)	1,265 (24.8)
Equivocal	19 (0.7)	13 (0.5)	32 (0.6)
HER2 IHC score prior to surgery (reported only if performed)			
0	856 (33.6)	881 (34.5)	1,737 (34.1)
1+	862 (33.8)	813 (31.9)	1,675 (32.8)
2+	464 (18.2)	480 (18.8)	944 (18.5)
3+	5 (0.2)	5 (0.2)	10 (0.2)
Unknown	21 (0.8)	21 (0.8)	42 (0.8)
ER/PR combination status			
ER+/PR+	2,172 (85.2)	2,132 (83.5)	4,304 (84.4)
ER+/PR−	359 (14.1)	392 (15.4)	751 (14.7)
ER−/PR+	3 (0.1)	12 (0.5)	15 (0.3)
ER+/UNK	10 (0.4)	13 (0.5)	23 (0.5)
UNK/PR+	2 (0.1)	2 (0.1)	4 (0.1)
UNK/PR−	1 (0.0)	1 (0.0)	2 (0.0)
UNK/UNK	2 (0.1)	0	2 (0.0)
AJCC 8th edition anatomic stage			
Stage I	9 (0.4)	5 (0.2)	14 (0.3)
Stage II	1,011 (39.7)	1,034 (40.5)	2,045 (40.1)
Stage III	1,528 (59.9)	1,512 (59.2)	3,040 (59.6)
Missing	1 (0.0)	1 (0.0)	2 (0.0)
N status for subgroup analysis used in AJCC stage derivation			
N0	285 (11.2)	328 (12.9)	613 (12.0)
N1–N3	2,261 (88.7)	2,219 (87.0)	4,480 (87.8)

Baseline disease characteristics	RIB + ET N=2,549, n (%)	ET only N=2,552, n (%)	Total N=5,101, n (%)
>N3	0	0	0
Missing	3 (0.1)	5 (0.2)	8 (0.2)
Time since initial diagnosis (months)			
N	2,517	2,528	5,045
Mean (SD)	11.8 (3.53)	11.8 (3.58)	11.8 (3.55)
Genomic tests			
Endopredict	23 (0.9)	28 (1.1)	51 (1.0)
Mammaprint	46 (1.8)	51 (2.0)	97 (1.9)
Oncotype DX	120 (4.7)	129 (5.1)	249 (4.9)
PAM50	38 (1.5)	29 (1.1)	67 (1.3)
Other	109 (4.3)	103 (4.0)	212 (4.2)

Table 103 Baseline prior treatment characteristics of patients in studies included for the comparative analysis of efficacy and safety

Baseline prior treatment characteristics	RIB + ET N=2,549, n (%)	ET only N=2,552, n (%)	Total N=5,101, n (%)
Number of patients who received any prior antineoplastic medication	2,423 (95.1)	2,439 (95.6)	4,862 (95.3)
CT	2,249 (88.2)	2,245 (88.0)	4,494 (88.1)
Anthracyclines	2,014 (79.0)	2,037 (79.8)	4,051 (79.4)
Taxanes	2,147 (84.2)	2,132 (83.5)	4,279 (83.9)
Other	2,190 (85.9)	2,189 (85.8)	4,379 (85.8)
ET	1,824 (71.6)	1,801 (70.6)	3,625 (71.1)
AI	1,601 (62.8)	1,592 (62.4)	3,193 (62.6)
Anti-estrogens	344 (13.5)	341 (13.4)	685 (13.4)
Gonadotropin-releasing hormone analogs	670 (26.3)	620 (24.3)	1,290 (25.3)
Therapy setting			
Adjuvant	2,160 (84.7)	2,150 (84.2)	4,310 (84.5)
Adjuvant chemotherapy	1,223 (48.0)	1,220 (47.8)	2,443 (47.9)
Neo-adjuvant	1,129 (44.3)	1,148 (45.0)	2,277 (44.6)
Neo-adjuvant chemotherapy	1,085 (42.6)	1,095 (42.9)	2,180 (42.7)
Number of patients who received any prior anti-neoplastic radiotherapy	2,292 (89.9)	2,302 (90.2)	4,594 (90.1)

Baseline prior treatment characteristics	RIB + ET N=2,549, n (%)	ET only N=2,552, n (%)	Total N=5,101, n (%)
Time since end of last radiotherapy (months)			
n	2,292	2,302	4,594
Mean (SD)	3.1 (2.48)	3.1 (2.50)	3.1 (2.49)
Median (Min;Max)	2.3 (0; 14)	2.3 (0; 14)	2.3 (0; 14)
Location of last radiotherapy			
Breast	1,035 (40.6)	1,004 (39.3)	2,039 (40.0)
Chest wall	1,209 (47.4)	1,210 (47.4)	2,419 (47.4)
Axillary lymph node	1,010 (39.6)	973 (38.1)	1,983 (38.9)
Supraclavicular lymph node	1,066 (41.8)	1,079 (42.3)	2,145 (42.1)
Internal mammary lymph node	374 (14.7)	410 (16.1)	784 (15.4)
Other	287 (11.3)	310 (12.1)	597 (11.7)
Duration of prior ET (months)			
n	1,818	1,795	3,613
Mean (SD)	3.5 (2.74)	3.6 (2.95)	3.5 (2.84)
Median (min; max)	2.8 (0; 16)	2.9 (0; 54)	2.9 (0; 54)
Number of patients who received any prior surgery	2,548 (100)	2,552 (100)	5,100 (100)
Time since end of last surgery (months)			
n	2,548	2,552	5,100
Mean (SD)	7.9 (3.80)	7.9 (3.76)	7.9 (3.78)
Median (min; max)	7.9 (0; 18)	7.8 (0; 21)	7.8 (0; 21)
Type of surgery			
Biopsy	679 (26.6)	673 (26.4)	1,352 (26.5)
Not biopsy	2,542 (99.7)	2,549 (99.9)	5,091 (99.8)

L.2 Subgroup analysis – additional information

Anatomic stage

In the subgroup of patients with anatomic stage II eBC, 62/1,012 (6.1%) iDFS events were observed in the RIB + ET arm and 96/1,034 (9.2%) in the ET only arm, corresponding to an iDFS hazard ratio of 0.644 (95% CI, 0.468−0.887). The 4-year iDFS rates were 93.9% (95% CI, 92.1%−95.3%) and 89.6% (95% CI, 87.4%−91.5%), respectively, reflecting a 4.3% absolute benefit favoring RIB + ET at a median follow-up of 47.4 months (8, 9).

In patients with anatomic stage III eBC, 200/1,527 (13.1%) iDFS events were observed in the RIB + ET arm and 244/1,512 (16.1%) in the ET only arm, corresponding to an iDFS hazard ratio of 0.737 (95% CI, 0.611−0.888). The 4-year iDFS rates were 84.3% (95% CI, 82.0%−86.3%) and 78.4% (95% CI, 75.6%−80.9%), respectively, 0

events were observed in the RIB + ET arm and 137/1,132 (12.1%) in the ET only arm, corresponding to an iDFS hazard ratio of 0.677 (95% CI, 0.523−0.877). The 4-year iDFS rates were 90.7% (95% CI, 88.7%−92.4%) and 85.3% (95% CI, 82.7%−87.6%), respectively, reflecting a 5.4% absolute benefit favoring RIB + ET (8, 9).

In postmenopausal women, 164/1,424 (11.5%) iDFS events were observed in the RIB + ET arm and 203/1,420 (14.3%) in the ET only arm, corresponding to an iDFS hazard ratio of 0.760 (95% CI, 0.619−0.933). The 4-year iDFS rates were 86.8% (95% CI, 84.7%−88.6%) and 82.2% (95% CI, 79.7%−84.4%), respectively, reflecting a 4.6% absolute benefit favoring RIB + ET (Table 104) (8, 9).

Menopausal status

In the subgroup of premenopausal women and men, 99/1,125 (8.8%) iDFS events were observed in the ribociclib plus ET arm and 137/1,132 (12.1%) in the ET only arm, corresponding to an iDFS hazard ratio of 0.677 (95% CI, 0.523−0.877). The 4-year iDFS rate was 90.7% (95% CI, 88.7%−92.4%) vs. 85.3% (95% CI, 82.7%−87.6%), reflecting a 5.4% absolute benefit favoring ribociclib plus ET.

In postmenopausal women, 164/1,424 (11.5%) iDFS events were observed in the ribociclib plus ET arm and 203/1,420 (14.3%) in the ET only arm, corresponding to an iDFS hazard ratio of 0.760 (95% CI, 0.619.-0.933). The 4-year iDFS rate was 86.8% (95% CI, 84.7%−88.6%) vs. 82.2% (95% CI, 79.7-84.4%), reflecting a 4.6% absolute benefit favoring ribociclib plus ET (Table 104) (8, 9).

Nodal status

In the subgroup of patients without nodal involvement (N0), 23/285 (8.1%) iDFS events were observed in the RIB + ET arm and 38/328 (11.6%) in the ET only arm, corresponding to an iDFS hazard ratio of 0.666 (95% CI, 0.397−1.118). The 4-year iDFS rates were 92.1% (95% CI, 88.1%−94.9%) and 87.0% (95% CI, 82.4%−90.5%), respectively, reflecting a 5.1% absolute benefit favoring RIB + ET at a median follow-up of 49.1 months (8, 9).

The study included N0 patients equivalent to their share in the overall target population, resulting in relatively small subgroup with only ≈ 13 % of the patients in the study. The study was not powered to claim superiority in subgroups. Although the subgroup did not reach nominal statistical significance, there is no interaction between nodal status and efficacy. Furthermore, there are no biological rationale supporting differences in efficacy across nodal status, which is also reflected in the EMA indication covering all high-risk EBC patients regardless of nodal status. It should be noted that the N0 target population would have to have T3-T4 tumors or T2 with additional high-risk features (grade 3 or grade 2 with high genomic risk). Exclusion of this group is deemed inappropriate, as the DBCG registry data clearly demonstrates these patients have an equivalent risk of recurrence, and the trial data demonstrates consistent efficacy regardless of nodal status.

In patients with nodal disease (N1–N3), 240/2,261 (10.6%) iDFS events were observed in the RIB + ET arm and 301/2,219 (13.6%) in the ET only arm, corresponding to an iDFS hazard ratio of 0.731 (95% CI, 0.617−0.866). The 4-year iDFS rates were 88.0% (95% CI, 86.4%−89.4%) and 83.0% (95% CI, 81.0%−84.8%), respectively, reflecting a 5.0% absolute benefit favoring RIB + ET at a median follow-up of 44.2 months (Table 104) (8, 9).

Table 104 iDFS: Subgroup analysis according to stage, menopausal status, and nodal status

iDFS	RIB + ET	ET only
Anatomic stage		
Stage II	N=1,012	N=1,034
Events, n (%)	62 (6.1)*	96 (9.2)*
Hazard ratio (95% CI)	0.644 (0.468−0.887)	Comparator
4-year rates, % (95% CI)	93.9 (92.1−95.3)	89.6 (87.4−91.5)
Stage III	N=1,527	N=1,512
Events, n (%)	200 (13.1)*	244 (16.1)*
Hazard ratio (95% CI)	0.737 (0.611−0.888)	Comparator
4-year rates, % (95% CI)	84.3 (82.0−86.3)	78.4 (75.6−80.9)
Menopausal status		
Premenopausal women and men	N=1,125	N=1,132
Events, n (%)	99 (8.8)*	137 (12.1)*
Hazard ratio (95% CI)	0.677 (0.523−0.877)	Comparator
4-year rates, % (95% CI)	90.7 (88.7−92.4)	85.3 (82.7−87.6)
Postmenopausal	N=1,424	N=1,420
Events, n (%)	164 (11.5)*	203 (14.3)*
Hazard ratio (95% CI)	0.760 (0.619−0.933)	Comparator
4-year rates, % (95% CI)	86.8 (84.7−88.6)	82.2 (79.7−84.4)
Nodal status		
N0	N=285	N=328

iDFS	RIB + ET	ET only
Events, n (%)	23 (8.1)*	38 (11.6)*
Hazard ratio (95% CI)	0.666 (0.397–1.118)	Comparator
4-year rates, % (95% CI)	92.1 (88.1–94.9)	87.0 (82.4–90.5)
N1–3	N=2,261	N=2,219
Events, n (%)	240 (10.6)*	301 (13.6)*
Hazard ratio (95% CI)	0.731 (0.617–0.866)	Comparator
4-year rates, % (95% CI)	88.0 (86.4–89.4)	83.0 (81.0–84.8)

Abbreviations: CI: Confidence Interval; iDFS: Invasive Disease-Free Survival; N0: Without Nodal Involvement; N1–3: One to Three Positive Nodes; NSAI: Nonsteroidal Aromatase Inhibitors;*% calculated. Source: Novartis Data on File (4-year landmark Analysis). (8, 9)

Non-overlapping population – Patients Not Meeting MonarchE Cohort 1 Eligibility

The eligibility criteria of monarchE cohort 1 were used as an exclusion criterion to establish a non-overlapping population, which is unique to NATALEE ([redacted]), hereafter referred to as the non-overlapping population. This patient population includes primarily N0 patients and N1 patients who were not allowed to be included in the monarchE study. Results from iDFS, DDFS, DRFS and OS are presented below. Endpoint analysis follows the same methodology as specified for all other efficacy analyses presented in the application.

The subgroup analysis of the non-overlapping population is provided per request and is not predefined. Consequently, NATALEE was not adequately powered for this analysis and interpretation of the results should be made with caution. With this limitation taken into consideration, [redacted].

Table 105: Efficacy results in the ITT compared to the non-overlapping population

Population	RIB + ET, %	ET, %	4-y abs. benefit, %	HR (95%CI)
iDFS, ITT	88.5	83.6	4.9	0.715 (0.609–0.840)
iDFS, non-overlapping	[redacted]	[redacted]	[redacted]	[redacted]
DDFS, ITT	89.4	84.9	4.5	0.715 (0.604–0.847)
DDFS, non-overlapping	[redacted]	[redacted]	[redacted]	[redacted]
DRFS, ITT	[redacted]	[redacted]	[redacted]	[redacted]
DRFS, non-overlapping	[redacted]	[redacted]	[redacted]	[redacted]
OS, ITT	95.0	94.2	0.8	0.827 (0.636–1.074)
OS, non-overlapping	[redacted]	[redacted]	[redacted]	[redacted]

[redacted] (Table 106, Figure 53).

[redacted]

Table 106: Type of first iDFS event in non-overlapping population

Type of first iDFS event*	RIB + ET	ET only
Invasive ipsilateral breast tumor	[redacted]	[redacted]
Invasive contralateral breast cancer	[redacted]	[redacted]
Death	[redacted]	[redacted]
Second primary non-breast invasive cancer	[redacted]	[redacted]
Local/regional invasive recurrence	[redacted]	[redacted]
Distant recurrence	[redacted]	[redacted]

[redacted]

Figure 53: Relative distribution of iDFS events, non-overlapping population

Table 107: List of deaths reported as AEs in non-overlapping population

Death, PT	RIB + ET	ET only
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		

[redacted]

Table 108: Subgroup analysis for non-overlapping population compared to ITT

	RIB + ET	ET only
iDFS		
Non-overlapping population	[redacted]	[redacted]
Events, n (%)	[redacted]	[redacted]
Hazard ratio (95% CI), p-value	[redacted]	
4-year rates, % (95% CI)	[redacted]	[redacted]
ARR*, %	[redacted]	[redacted]
ITT	N= 2,549	N=2,552
Events, n (%)	263 (10.3)	340 (13.3)
Hazard ratio (95% CI)	0.715 (0.609–0.840), p <0.0001	
4-year rates, % (95% CI)	88.5 (87.1–89.8)	83.6 (81.8–85.2)
ARR (%)	4.9	Comparator
DDFS		
Non-overlapping population	[redacted]	[redacted]
Events, n (%)	[redacted]	[redacted]

	RIB + ET	ET only
Hazard ratio (95% CI), p-value	[redacted]	
4-year rates, % (95% CI)	[redacted]	[redacted]
ARR	[redacted]	[redacted]
ITT	N= 2,549	N=2,552
Events, n (%)	240 (9.4)	311 (12.2)
Hazard ratio (95% CI), p-value	0.715 (0.604–0.847), p <0.0001	
4-year rates, % (95% CI)	89.4 (88.0–90.7)	84.9 (83.2–86.5)
ARR (%)	4.5	Comparator
DRFS		
Non-overlapping	[redacted]	[redacted]
Events, n (%)	[redacted]	[redacted]
Hazard ratio (95% CI), p-value	[redacted]	
4-year rates, % (95% CI)	[redacted]	[redacted]
ARR (%)	[redacted]	
ITT	N= 2,549	N=2,552
Events, n (%)	[redacted]	[redacted]
Hazard ratio (95% CI), p-value	[redacted]	
4-year rates, % (95% CI)	[redacted]	
ARR (%)	[redacted]	[redacted]
OS		
Non-overlapping	[redacted]	[redacted]
Events, n (%)	[redacted]	[redacted]
Hazard ratio (95% CI), p-value	[redacted]	
4-year rates, % (95% CI)	[redacted]	[redacted]
ARR (%)	[redacted]	[redacted]
ITT	N= 2,549	N=2,552
Events, n (%)	105 (4.1)	121 (4.7)
Hazard ratio (95% CI), p-value	0.827 (0.636–1.074), p = 0.0766	
4-year rates, % (95% CI)	95.0 (94.0–95.9)	94.2 (93.0–95.2)
ARR	0.8	Comparator

*ARR: absolute risk reduction. p-value based on Cox-regression analysis

Figure 54: Kaplan-Meier for iDFS - non-overlapping population

Figure 55 Kaplan-Meier for DDFS - non-overlapping population -

Figure 56 Kaplan-Meier for DRFS - non-overlapping population

Figure 57 Kaplan-Meier for OS - non-overlapping population

Overlapping population – Patients Meeting MonarchE Cohort 1 Eligibility

The eligibility criteria of monarchE cohort 1 were used as an inclusion criterion to establish a overlapping population ([redacted]), hereafter referred to as the overlapping population. Results from iDFS, DDFS and OS are presented below. Endpoint analysis follows the same methodology as specified for all other efficacy analyses presented in the application.

The subgroup analysis of the overlapping population is provided per request and is not predefined. [redacted]

Table 109 Subgroup analysis for non-overlapping population

	RIB + ET	ET only
iDFS		
Overlapping population	[redacted]	[redacted]
Events, n (%)	[redacted]	[redacted]
Hazard ratio (95% CI), p-value	[redacted]	
4-year rates, % (95% CI)	[redacted]	[redacted]
ARR*, %	[redacted]	[redacted]
DDFS		
Overlapping population	[redacted]	[redacted]
Events, n (%)	[redacted]	[redacted]
Hazard ratio (95% CI), p-value	[redacted]	
4-year rates, % (95% CI)	[redacted]	[redacted]
ARR	[redacted]	[redacted]
OS		
Overlapping population	[redacted]	[redacted]
Events, n (%)	[redacted]	[redacted]
Hazard ratio (95% CI), p-value	[redacted]	
4-year rates, % (95% CI)	[redacted]	[redacted]
ARR (%)	[redacted]	[redacted]

Table 110 Kaplan-Meier for iDFS - overlapping population (monarchE)

Table 111 Kaplan-Meier for DDFS - overlapping population (monarchE)

Table 112 Kaplan-Meier for OS - overlapping population (monarchE)

L.3 Adverse events of grade 3-5 severity

In the table below, we present the most common grade 3-5 adverse events from the NATALEE trial from the 4-year landmark analysis. Please see section 9 for a description of the adverse events and safety profiles of RIB + ET and ET only from the NATALEE trial.

Table 113 Most common grade 3–5 adverse events, irrespective of causality, by preferred term and severity (least 1% incidence in either arm). Source: Novartis data on file (9).

	RIB + ET (N=2,526)				ET only (N=2,441)			
	Grade ≥3 n (%)	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**Grade ≥3 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
Number of patients with at least one TEAE	1,622 (64.2)	1,471 (58.2)	140 (5.5)	11 (0.4)	481 (19.7)	437 (17.9)	40 (1.6)	4 (0.2)
Neutropenia	710 (28.1)	674 (26.7)	36 (1.4)	0	13 (0.5)	12 (0.5)	1 (<0.1)	0
Neutrophil count decreased	448 (17.7)	428 (16.9)	20 (0.8)	0	8 (0.3)	6 (0.2)	2 (0.1)	0
ALT increased	194 (7.7)	161 (6.4)	33 (1.3)	0	17 (0.7)	16 (0.7)	1 (<0.1)	0
AST increased	117 (4.6)	101 (4.0)	16 (0.6)	0	14 (0.6)	14 (0.6)	0	0
WBC decreased	95 (3.8)	93 (3.7)	2 (0.1)	0	6 (0.2)	5 (0.2)	1 (<0.1)	0
Leukopenia	94 (3.7)	94 (3.7)	0	0	2 (0.1)	2 (0.1)	0	0
Hypertension	59 (2.3)	59 (2.3)	0	0	64 (2.6)	64 (2.6)	0	0
Gamma-glutamyl transferase increased	25 (1.0)	22 (0.9)	3 (0.1)	0	22 (0.9)	22 (0.9)	0	0
Arthralgia	25 (1.0)	25 (1.0)	0	0	31 (1.3)	31 (1.3)	0	0
Lipase increased	25 (1.0)	18 (0.7)	7 (0.3)	0	13 (0.5)	7 (0.3)	6 (0.2)	0

L.4 All deaths by primary reason for death and preferred term

The table presents all deaths including death due to recurrence/progression. Deaths also includes those not considered on-treatment deaths and not related to treatment. Includes deaths with cause other than AE (other category and death due to disease recurrence/progression).

Table 114

Preferred term	RIB + ET, n = 2526	ET only, n = 2441
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Grey rows, marks the system organ class of deaths due to AE. [redacted]. The rows: “Disease Recurrence/Progression”, “Death due to adverse event”, and “other category” combined equals the total number of patients who died. Other category reflects death due to existing general health deterioration or aging. The number of deaths is different per safety set and per full analysis set (ITT) of OS efficacy analysis. This

is mainly because the grouping rule of the safety set. Only patients took at least one dose of RIB will be grouped in RIB + ET. However, for the full analysis set, the grouping is per randomization.

Appendix M. Indirect Treatment Comparisons of Ribociclib plus ET vs. Abemaciclib plus ET

To inform the inclusion of comparators for cost-effectiveness evaluations of RIB + ET for submissions to HTA agencies, ITCs of the efficacy and safety of RIB + ET vs other interventions of interest for patients with HR+/HER2− eBC were conducted. The following is a summary of the ITC of RIB + ET compared to abemaciclib + ET, presenting the relevant results. As per request from the DMC, the full ITC is attached to this application as a separate document (confidential).

This analysis included ITCs of RIB + ET and ET alone in the NATALEE trial vs abemaciclib plus ET and ET alone in the monarchE trial. The feasibility assessment determined that an unanchored MAIC was the most robust approach for comparing RIB + ET vs abemaciclib plus ET in the population of interest, which served as the primary analysis. Additionally, an anchored ITC was also determined to be feasible for one of the outcomes of interest in a subgroup of patients (107, 111). Briefly, the approach for the primary analysis was determined based on the findings from the feasibility assessment that included a disconnected evidence network due to the lack of a common comparator in the NATALEE and monarchE control arms and differences in the trial populations.

The ITCs used individual patient data (IPD from the NATALEE trial of RIB + ET and aggregate data reported for Cohort 1 (high-risk disease) of the monarchE trial of abemaciclib plus ET (99, 112-115). Unanchored MAICs were conducted using procedures described by Signorovitch and the NICE Decision Support Unit (DSU) Technical Support Document (TSD) Number 18 (111, 116, 117).

M.1 Feasibility assessment

Study designs

[redacted]

Eligibility criteria

[redacted]

For reference an overview of the populations are presented in the figure below.

Figure 58 Overview of NATALEE and monarchE inclusion criteria based on TNM staging and other risk factors

AJCC Anatomical Staging	TN (M0)	NATALEE	monarchE
Stage IIA	T0N1		Only if grade 3 or Ki-67 ≥20%
	T1N1		Only if grade 3 or Ki-67 ≥20%
	T2N0	Only if G3; or G2 with Ki-67 ≥20% or high genomic risk[a]	
Stage IIB	T2N1		Only if grade 3 or Ki-67 ≥20%
	T3N0		
Stage IIIA	T0N2		
	T1N2		
	T2N2		
	T3N1		
	T3N2		
Stage IIIB	T4N0		
	T4N1		Only if tumor size ≥5 cm or grade 3 or Ki-67 ≥20%
	T4N2		
Stage IIIC	Any TN3		

NATALEE included:
- All **N1**, **N2**, **N3**
- **N0**: **T2** [(*G2 + high genomic risk or Ki-67≥ 20%) or G3*)], **T3, T4**

monarchE included:
- All **N2**, **N3**
- **N1** only if G3 or tumor size ≥ 5cm or Ki-67≥20%

- **N0 was not included in monarchE**

Baseline Characteristics

[redacted]

[redacted]

[redacted]

Outcome definitions

[redacted]

M.1.1 Conclusion

[redacted]

M.2 Analyses conducted

[redacted]

M.2.1 Primary analysis

[redacted]

Supportive analysis/Exploratory analysis

[redacted]

M.3 Methodology

[redacted]

M.4 Current MAIC Results

M.4.1 Primary analysis

[redacted]

[redacted]

[redacted]

Figure 59 Primary analysis: Histogram of MAIC weights

Abbreviations: ET: ET; MAIC: Matching-Adjusted Indirect Comparison.

Table 115 Primary analysis: Summary of MAIC weights

Characteristic	RIB + ET	ET only
N	[redacted]	[redacted]
ESS	[redacted]	[redacted]
Percent change in sample size	[redacted]	[redacted]
Maximum weight	[redacted]	[redacted]

Abbreviations: ESS: Effective Sample Size; ET: ET; MAIC: Matching-Adjusted Indirect Comparison.

[redacted]

M.4.2 Efficacy outcomes: Primary Analyses

[redacted]

[redacted]

[redacted]

Table 116 RIB + ET vs abemaciclib plus ET: MAIC efficacy results (primary ITC analysis, base case)

	Before matching, unweighted comparison, Hazard ratio (95% CI)	After matching, MAIC, Hazard ratio (95% CI)
iDFS	[redacted]	[redacted]
DRFS	[redacted]	[redacted]
OS	[redacted]	[redacted]

Abbreviations: AI: Aromatase Inhibitor; CI: Confidence Interval; DRFS: Distant Relapse-Free Survival; ET: ET; iDFS: Invasive Disease-Free Survival; ITC: Indirect Treatment Comparison; MAIC: Matching-Adjusted Indirect Comparison; OS: Overall Survival.

M.4.3 Safety outcomes: Primary Analyses

[redacted]

Table 117 Primary analysis: Comparison of TEAEs

AE	Events rates				RIB + ET vs Abema + ET			
	NATALEE		monarchE			95% CI		
	RIB + ET (%)	ET (%)	ABE + ET (%)	ET (%)	OR	Lower	Upper	P-value
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								

Abbreviations: Abema: Abemaciclib; AE: Adverse Event; ALT: Alanine Aminotransferase; CI: Confidence Interval; ET: ET; OR: Odds Ratio; RIB: Ribociclib; TEAE: Treatment-Emergent Adverse Event. **Bold font** indicates statistically significant results; OR <1 means that the results were in favor of RIB + ET; OR >1 means that the results were in favor of Abema + ET. Note: Event rates equal to zero were adjusted with continuity correction to allow for estimation of ORs via logistic regression.

Narrative comparison of important differences in safety

Ribociclib and abemaciclib have been shown to be well-tolerated for the treatment of HR+/HER2− BC, with distinct toxicity profiles for each CDK4/6i across the advanced BC (ABC) and early BC setting (5, 120, 121).

Higher rates of severe gastrointestinal adverse events (AEs) and fatigue were observed in patients treated with abemaciclib + ET vs ET alone; patients treated with ribociclib

reported higher rates of hematologic AEs, neutropenia, elevated liver enzymes, and rare cases of QTc prolongation vs ET alone (121).

In NATALEE, the most common AE associated with ribociclib was neutropenia (any grade, 62.8%; grade ≥ 3, 44.4%) (9); in monarchE, diarrhea was the most common AE associated with abemaciclib (any grade, 83.6%; grade ≥ 3, 7.8%) (121).

In the NATALEE trial, the most common AEs that led to discontinuation were elevated liver enzymes and arthralgia, and for monarchE, it was diarrhea. With ribociclib, the 400-mg starting dose investigated in the eBC setting was associated with lower rates of neutropenia and QTc prolongation compared with the 600-mg dose, which is the SOC dose in the ABC setting (121).

Protocol differences:

In the NATALEE protocol it was mandatory to discontinue ribociclib if AEs were not resolved within 28 days, whereas in monarchE it was up to the individual investigator when to discontinue treatment (44). Also, only one dose reduction step was possible, from 400 mg to 200 mg, vs. 2 dose reductions steps in monarchE. The rate of discontinuation due to AEs is the same between the trials (NATALEE 19.7% vs. monarchE 18.5% despite primary differences between the two protocols regarding criteria for AE handling (9, 120).

Distinct toxicities: Liver toxicities vs. venous thromboembolic events (VTEs)

In NATALEE liver related toxicities were reported (any grade 26.7% and grade ≥3 8.6%). Most discontinuations in the NATALEE study were due to liver related AEs (8.9%), which were asymptomatic (lab abnormalities) and resolved with dose reductions or discontinuations (9).

In monarchE venous thromboembolic events (VTEs) were reported, which were higher with abemaciclib + ET versus ET. In the abemaciclib arm, increased VTE risk was observed with tamoxifen versus aromatase inhibitors (4.3% versus 1.8%) (122).

Symptomatic vs asymptomatic AEs

Abemaciclib has a high incidence of all-grade diarrhea, which is symptomatic and has a considerable impact on patients' lives. All-grade diarrhea was 83.5%, grade ≥3 diarrhea was 7.8% (120).

Majority of grade ≥3 AEs in NATALEE were laboratory findings that were identifiable, manageable, and reversible (9).

M.5 Conclusion

[redacted]

Appendix N. Cost comparison ribociclib vs. abemaciclib

Due to the updated request, this section has been revised and is now based on calculations from the submitted cost-effectiveness model, which has been updated to include a cost-minimization model, comparing ribociclib + ET with abemaciclib + ET.

N.1 Cost of medicine

The list of medicines, dosing and the pharmacy purchase Prices (PPP) is presented in Table 118. Ribociclib is available in three package sizes (21, 42 and 63 tablets) with a consistent tablet size of 200 mg regardless of package. The chosen 42 tablet package size is in line with the SmPC recommended posology in the adjuvant setting (400 mg). The chosen package size of abemaciclib was chosen as the starting dose as per SmPC recommended posology in the adjuvant treatment setting (150 mg). The add-on treatment for both ribociclib and abemaciclib was set equal under the assumption, that the overlapping population would be treated with the same ET backbone. The user has the option to use the add-on treatment patients received in monarchE for the abemaciclib plus ET arm.

Table 118 Cost of medicine

Medicine	Dose	PPP, DKK	Relative dose intensity	Frequency	Vial sharing
Ribociclib	400 mg	15,537	83.40 %	21 days on 7 days off Max 3 years	NA
Abemaciclib	150 mg	18,077	100%	QD Max 2 years	NA
Letrozole	2.5 mg	34	99.03 %	QD	NA
Anastrozole	1 mg	38	99.03 %	QD	NA
Goserelin	3.6 mg	1,280	101.37 %	Implant every 3rd month	NA
Exemestane	25 mg	3,680	100 %	QD	NA
Tamoxifen	20 mg	150	100 %	QD	NA

Source: Medicinpriser.dk

The model considers medicine waste separately for abemaciclib. In monarchE 43.7% had one dose reduction and 13.9% had two reductions, which was assumed to equal the cost of half a pack per dose reduction (63). Half-cycle correction is not applied to the TTD curve (as per DMC guidelines) and thus wastage stemming from unused last packages is included. Dosing of ribociclib in the eBC setting consist of 400 mg QD (200 mg x 2). As such, down dosing does not require the purchase of a new package, and no wastage is assumed

due to down dosing. Since there is no wastage, the RDI from NATALEE of 333.58 mg has been used, which equates to 83.4%. An RDI of 100% was used for abemaciclib, as packages cannot be reused and since packages have a flat price. An arbitrary time spent off treatment was added for abemaciclib, since days where patients are off treatment wouldn't incur costs in a real-life setting. This was not included for ribociclib, since this is covered by the RDI measurement. The time on treatment was taken from NATALEE (9), where the TTD KM curve was used. For Abemaciclib, the data reported in Rugo et al. was used (61).

N.2 Adverse events

Adverse events were included in the cost-comparison, despite having little impact on the overall results. The rates were taken from the two registration trials NATALEE and monarchE and used DRG rates consistent with the DMC assessment of abemaciclib (9, 28, 80). We do note that the cost of treating diarrhea is likely higher in a real-world setting, since hospitalization should be considered already with grade 3 diarrhea (CTCAE 5.0 criteria defines grade 3 diarrhea as: "Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL" (123). It was assumed all adverse events would occur in the first year of treatment and is therefore not discounted. Below is a table of the costs and proportion of patients experiencing AEs, which results in DKK 913.09 per average ribociclib patient and DKK 1,472.01 per average abemaciclib patient.

Table 119 Adverse event costs for ribociclib and abemaciclib

Adverse event	Ribociclib + ET	Abemaciclib + ET	Cost per event / DKK
ALT	7.68 %	2.76 %	1,957
Diarrhea	0.63 %	7.85 %	7,818
Leukopenia	3.72 %	11.39 %	2,208
Lymphopenia	0.48 %	5.41 %	2,208
Neutropenia	28.11 %	19.63 %	2,208

N.3 Follow-up costs

One of the main differences between ribociclib and abemaciclib is the maximum treatment length, which is 3 and 2 years for ribociclib and abemaciclib, respectively.

During treatment, patients incur follow-up costs and thus, ribociclib will be associated with higher follow up costs. The time spent in iDFS was set equal between the two arms and thus, the only follow-up cost difference between the two treatments, is the additional time spent on treatment for ribociclib. Cost of follow up was kept equal to that of the submitted cost-effectiveness analysis, and a 5-year horizon was used (after 3 years there is no cost-difference), which can be changed in the health economic model. Below is an overview of the cost of services and their frequency for all patients.

Table 120 Follow up services in the IDFS setting

Service/Treatment	Frequency	Utilization Rate	Source
Follow-Up Services			
Mammogram	Once a year during first 4 years	100%	KOL input
Oncologist Visit	Two times in the first year, one time in year two and year three	100%	KOL input
Patient time cost per visit	Once a year	100%	KOL input
Transportation cost	Once a year	100%	KOL input
Mastectomy	One-off	30.1%	KOL input
Lumpectomy	One-off	69.9%	KOL input
Radiotherapy	One-off	90%	KOL input
PET/CT	One-off	100%	KOL input

Table 121 Additional follow-up services when on CDK4/6 treatment.

Service Name	Description
Complete blood count	12 times during first year, and four times year two and year three.
Liver function test	12 times during first year, and four times year two and year three.
Electrocardiogram	Twice during first year
Oncologist visit	10 times during first year, and three times in year two and year three
Patient time cost per visit	12 times during first year, and three times in year two and year three
Transportation cost	12 times during first year, and three times in year two and year three

Note: Patients on abemaciclib would not incur any of the costs in the third year of treatment

Table 122 Cost of services during follow-up

Activity	Unit cost [DKK]	DRG code / description	Reference
Mammogram	661	DRG 2025, 30PR14: Mammografi, ukompliceret	DRG 2025
Oncologist visit	1,578	09MA98: MDC09 1-dagsgruppe, pat. mindst 7 år	DRG 2025
Electrocardiogram	287.37	0101 + 7156	Honorartabel
Mastectomy	154,495	09MP01: Mastektomi med rekonstruktion med stilket lap og dobbeltsidig mastektomi med protese	DRG 2025

Activity	Unit cost [DKK]	DRG code / description	Reference
Lumpectomy	80,119	09MP02: Segmentresektion af bryst med onkoplastisk rekonstruktion og/el. kontralateral korrektion og enkeltsidig mastektomi med protese	DRG 2025
Radiotherapy	15,817	27MP13: Stråleplanlægning kompleks	DRG 2025
Patient time cost per visit	376	2 hour per contact	Værdisætning af enhedsomkostninger
Transportation cost	140.40	Average 40 km travel per visit used	Værdisætning af enhedsomkostninger
PET/CT	3,737	36PR37	DRG 2025

Source: DRG takster 2025, værdisætning af enhedsomkostninger (124).

Liver function test and complete blood count was not costed separately, since they were assumed to be included in the DRG rate of an outpatient visit.

N.4 Cost-minimization results

Using the methods described above, the total medicines costs, cost of adverse events, follow-up and monitoring costs, and patient and transportation costs are presented in Table 123 below, which compares the costs of ribociclib + endocrine therapy with abemaciclib + endocrine therapy for patients who are in the invasive-disease free state.

Table 123 Cost comparison of ribociclib versus abemaciclib

Follow-up cost	Ribociclib + ET	Abemaciclib + ET	Difference
Drug costs	[redacted]	[redacted]	[redacted]
Adverse events	913	1,472	-559
Follow-up and monitoring	95,834	89,508	6,325
Patient time and transportation costs	10,401	8,410	1,992
Total	[redacted]	[redacted]	[redacted]

N.5 Budget impact

The budget impact of introducing ribociclib, using PPP prices, including discounting of the results, are also presented with a year 5 budget impact of 930,930 DKK. Unsurprisingly, there is a large cost off-set in year 1 and year 2 of 16 and 29 million DKK, respectively. In year 3 and beyond, this stabilizes to approximately 1 million DKK. Below is a table showing the budget impact, from year 1 to year 5, in a setting where ribociclib is introduced to 100% of the 250 patients in the overlapping population.

Table 124 Budget impact of introducing Kisqali for the treatment of HR+/HER2- early breast cancer patients in Denmark, in the overlapping population.

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	-16,304,485	-29,169,506	-930,903	-930,903	-930,903
The medicine under consideration is NOT recommended	0	0	0	0	0
Total Budget impact	**-16 304 485**	**-29 169 506**	**-930 903**	**-930 903**	**-930 903**