Medicinrådet

Bilag til Medicinrådets vurdering af capivasertib til ER+/HER2-negativ lokalt fremskreden eller metastatisk brystkræft

Vers. 1.0

Bilagsoversigt

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

Medicinrådet
Dampfærgevej 21-23, 3. sal
2100 København

03.10.2025

Draft assessment report regarding capivasertib in combination with fulvestrant for 2nd line treatment of ER+/HER2 negative locally advanced or metastatic breast cancer

AstraZeneca would like to thank DMC for the assessment of capivasertib and appreciates the opportunity to comment on the draft report. AstraZeneca has the following comments that we would like to emphasize:

The application selects a clinically relevant sub-population of patients in CAPItello-291

The CAPItello-291 study included patients with locally advanced or metastatic ER+/HER2- breast cancer. The target population for this assessment is 2nd line patients that previously have received CDK4/6 inhibitors (CDK4/6i) in combination with endocrine therapy (ET) as the 1st line standard of care and that have one or more PIK3CA/AKT1/PTEN-alterations. Despite it being a treatable disease, mBC is still considered incurable and in general has a poor prognosis, a prognosis that is even worse for patients with gene mutations and prior exposure to CDK4/6is (as described in our dossier). By identifying a patient population from the study that experiences the highest unmet need in clinical practice and that achieves the largest benefit from the treatment, AstraZeneca is in line with the approach DMC recommends.

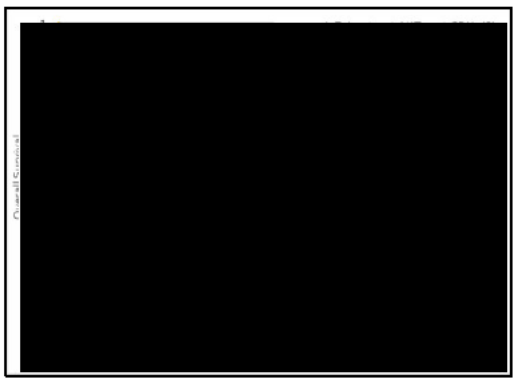
In the subpopulation in focus the improvement in median PFS was [redacted]) in favor of capivasertib in combination with fulvestrant [redacted]), thereby being statistically significant and exceeding the 3 months previously by DMC being considered as the minimum relevant clinical effect. An increase of [redacted]) in median OS was observed in favor of capivasertib + fulvestrant [redacted]. The minimum clinical effect previously defined by DMC on median OS was 3 months, [redacted]

The comparator arm of CAPItello-291 and its generalizability to the Danish 2nd line standard of care

DMC assumes that some 2nd line patients will receive fulvestrant, while others will be treated with chemotherapy (CT) (e.g., all patients with good PS and younger than 60 years). Furthermore, DMC assumes CT to be more efficacious than fulvestrant for the patient population in scope. Consequently, DMC consider the generalizability of the comparator arm in the study as uncertain to some extent, questioning the relative effect of capivasertib + fulvestrant vs the current standard of care in Denmark. However, AstraZeneca finds this uncertainty to be limited, as guideline recommendations make the 2nd line treatment choice dependent on clinical and patient parameters, which translates into following clinical scenarios in the absence of approved targeted therapies: patients who remain endocrine sensitive are likely considered for continued ET-based regimens such as fulvestrant, while early CT use is applicable for aggressive disease (e.g., fast progressors or patients with visceral crisis). Furthermore, to our knowledge, there is currently no evidence demonstrating any significant difference in efficacy between CT and fulvestrant for 2nd line ER+/HER2- mBC patients in the post CDK4/6i setting. To the contrary, various recent real-world evidence (RWE) studies (including data from Nordic settings) indicate similar outcomes for ET/fulvestrant and CT in the 2nd line post CDK4/6i setting:

- Giachetti et al. 2025 conclude that the choice between ET and CT post CDK4/6i did not significantly influence OS. This outcome was consistent for the overall population and for patients with and without visceral involvement (table 2 and 3 in the paper). [1]
- Karihtala et al. 2025 (similar study design as the RWE study presented in Appendix K in our original submission) report 2-year OS for CT and ET equal to 40.1% and 42.8%, respectively, based on a Finnish ER+/HER2- mBC patient population in the post CDK4/6i setting [2].

[redacted]



To further support this argument, AstraZeneca has extracted OS outcomes for a Danish ER+/HER2- mBC cohort treated with 2nd line CT after CDK4/6i to compare with OS outcomes from 2nd line patients treated with fulvestrant in the same cohort (study described in Appendix K in the application), as well as the control arm of the Capitello-291 trial for the subgroup in scope for this application. [redacted]

In a potential scenario analysis like the one investigated by DMC (i.e., comparing capivasertib with CT), outcomes should be at least similar to the base case analysis, considering similar OS outcomes for CT and fulvestrant, and higher CT related costs and dis-utilities due to side effect profile and potential intravenous administration.

Adaptions of patient age and therapy may overestimate patient numbers

In its assessment, DMC has increased the patient age in the base case to better reflect Danish clinical practice (68 instead of 57 years), yet also contends that younger patients (under 60) are more likely to receive CT. While AstraZeneca acknowledges age differences from real-world to study settings, these assumptions are yet not fully aligned with other rationales in the assessment. If the eligible population for capivasertib is assessed to be older, the share of CT use in this setting would be lower, with younger age being an indicator for CT use. Additionally, the proportion of patients that are expected to receive CT, e.g. due to high disease burden, is not adequately reflected in the DMCs estimated patient numbers used for modeling; this risks an overestimation of both the total number of patients tested and those potentially treated with capivasertib. Therefore, the patient population may be notably smaller than assumed in the DMC assessment.

Costs assumptions in the DMC base case model could overestimate real-world financial impact

The DMC removed subsequent treatment and terminal care costs, while increased testing costs contributing to increased incremental costs for capivasertib + fulvestrant vs. fulvestrant. These changes may not accurately reflect real-world practice or the true financial impact. By not including the costs of later treatments and terminal care, the analysis misses possible cost savings as patients receiving capivasertib may have lower overall cost. Furthermore, attributing the full AKT testing cost (DKK 4.500) exclusively to the capivasertib arm likely overestimates expenses, as AKT pathway analysis is typically included within broader NGS (next-generation sequencing) panels alongside other relevant genes or mutations as part of standard diagnostic practice, rather than performing full NGS testing solely to identify AKT pathway alterations. This means that introducing capivasertib does not necessarily incur isolated testing costs, and the incremental financial impact should be reconsidered.

Taken together, these assumptions may lead to an overestimation of costs for capivasertib and an underestimation of its potential positive impact on resource utilization. AZ would like to bring into attention that the incremental cost of introducing capivasertib in 2nd line would overall be limited.

We look forward to receiving the DMC decision with the hope that capivasertib will be made available as the first targeted treatment for patients with ER+/HER2- locally advanced or metastatic AKT pathway altered breast cancer. These patients after progression on 1st line CDK4/6i are currently in high unmet need, with limited availability of 2nd line treatment options and those available lacking considerable efficacy benefits or tolerability profiles. Providing access to this novel targeted medicine with proven benefit gives patients and healthcare providers a new chance for prolonged treatment response and postponing the use of CT to later lines.

Kind regards,

Mette Lange, Market Access Manager
Greta Bütepage, HTA manager

References

1. Giachetti, P.M., S; Gandini, S; Giudici, F; Marra, A; Nicolò, E; Zattarin, E; Corti, C; Boldrini, L; Verrazzo, A; Sposetti, C; Razeti, M; Schianca, A; Scafetta, R; Salimbeni, B; Esposito, A; Zagami, P; Trapani, D; Malagutti, B; Caputo, R; Vernieri, C; Munzone, E; Scagnoli, S; Botticelli, A; Lambertini, M; Giuliano, M; De Laurentiis, M; Viale, G; Bianchini, G; Curigliano, G; De Angelis, C; Criscitiello, C, *Survival Following CDK4/6 Inhibitor Therapy for Hormone Receptor–Positive, ERBB2–NegativeMetastatic Breast Cancer.* JAMA Network Open. 2025;8(2):e2461067, 2025.
2. Karihtala, P.T., S; Ågesen, T; Bütepage, G; Polyzoi, M; Lassenius, M;, *Healthcare Resource Utilization and Survival of Patients With HR+/HER2-negative Metastatic Breast Cancer After Treatment With CDK4/6-Inhibitors in Finland*. 2025.

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03.10.2025

DBS/MBA

Forhandlingsnotat

Dato for behandling i Medicinrådet	29.10.2025
Leverandør	AstraZeneca
Lægemiddel	Truqap (capivasertib)
Ansøgt indikation	Capivasertib i kombination med fulvestrant er indiceret til behandling af voksne patienter med østrogen receptor (ER)-positiv, HER2-negativ lokal fremskreden eller metastatisk brystkræft med en eller flere PIK3CA/AKT1/PTEN-mutationer efter tilbagefald eller progression på eller efter et endokrinbaseret behandlingsregime.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Truqap (capivasertib):

Tabel 1: Forhandlingsresultat – betinget pristilbud

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Truqap	160 mg x 64 stk.	41.034,97	[redacted]	[redacted]
Truqap	200 mg x 64 stk.	41.034,97	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

Hvis ikke Truqap anbefales af Medicinrådet, har Amgros aftalt følgende pris med leverandøren (jævnfør tabel 2):

Tabel 2: Forhandlingsresultat – ubetinget pristilbud

Lægemiddel	Styrke (pakning-størrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Truqap	160 mg x 64 stk.	41.034,97	[redacted]	[redacted]
Truqap	200 mg x 64 stk.	41.034,97	[redacted]	[redacted]

Aftaleforhold

[redacted] Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

Konkurrencesituationen

[redacted]

Tabel 3 viser lægemiddeludgifter i relation til andre lægemidler til brystkræft med PIK3CA-mutation.

*Tabel 3: Sammenligning af lægemiddeludgifter pr. patient per år**

Lægemiddel	Styrke (pakning-størrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Truqap	200 mg x 64 tabletter	400 mg (p.o.) to gange dagligt (800 mg i alt) i fire dage efterfulgt af tre dages pause	[redacted]	[redacted]
Piqray**	150 mg x 56 tabletter	300 mg (p.o.) en gang dagligt	[redacted]	[redacted]

*Både Truqap og Piqray er i kombination med fulvestrant og inkluderes derfor ikke i ovenstående tabel.
** [redacted]

Status fra andre lande

Tabel 4: Status fra andre lande

Land	Status	Link
Norge	Ikke anbefalet	Link til anbefaling
England	Anbefalet	Link til anbefaling
Sverige	Ikke vurderet nationalt	Link til status

Opsummering

[redacted]

Application for the assessment of Truqap (capivasertib) in combination with fulvestrant for adult patients with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following treatment with CDK4/6 inhibitors (CDK4/6i).

Submitted by AstraZeneca 23.05.2025

Re-submitted technical validation by AstraZeneca 10.06.2025

Re-submitted submission dossier by AstraZeneca 02.07.2025

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]

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Table of contents

Tables and Figures

Abbreviations

Abbreviation	Definiton
1L	1st line
2L	2nd line
3L	3rd line
aBC	Advanced breast cancer
ADC	Antibody drug conjugate
AE	Adverse event
AI	Aromatase inhibitor
AKT	(Also known as) Protein kinase B
ASCO	American Society of Clinical Oncology
BC	Breast cancer
CDK4/6i	Cyclin-dependent kinase 4/6 inhibitor
CEM	Cost-effectiveness model
CI	Confidence interval

CT	Chemotherapy
DFS	Disease-free survival
EMA	European Medicines Agency
EORTC	European Organization for Research & Treatment of cancer
EQ-5D-5L	EuroQoL 5 Dimensions 5 levels
EQ-VAS	EuroQoL visual analogue scale
ER	Estrogen receptor
ESMO	European Society for Medical Oncology
ET	Endocrine treatment/therapy
FAS	Full analysis set
FDA	Food and Drug Administration
GRD	Global reimbursement dossier
HDAC	Histone deacetylase
HEPE	Health Economic & Payer Evidence
HER2	Human epidermal growth factor receptor 2
HR	Hormone receptor
HR	Hazard ratio
HRQoL	Health Related Quality of Life
HSUV	Health state utilities values
IQR	Interquartile range
ITC	Indirect treatment comparison
ITT	Intention to treat
Ki67	Antigen Kiel 67
KM	Kaplan-Meier
MAIC	Matching-adjusted indirect comparison
MAPK	Mitogen Activated Protein kinase
mBC	Metastatic breast cancer
MMRM	Mixed effects repeated measures regression

mTOR	Mammalian target of rapamycin
NCCN	National Comprehensive Cancer Network
NGS	Next generation sequencing
NMA	Network meta-analysis
NR	Not reported
NSAI	Non-steroidal aromatase inhibitor
OS	Overall survival
PI3K	Phosphoinositide 3-kinase
PFS	Progression-free survival
PH	Proportional hazards
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PR	Progesterone receptor
PROs	Patient-reported outcomes
PS	Performance status
PSM	Partitioned survival model
PTEN	Phosphatase and tensin homolog
Raf protein	Rapidly Accelerated Fibrosarcoma protein
Ras protein	Rat sarcoma virus protein
RECIST	Response Evaluation Criteria in Solid Tumours
RMST	Restricted mean survival time
RWE	Real world evidence
SAP	Statistical analysis plan
SAS	Safety analysis set
SLR	Systematic literature review
SOC	Standard of care
TFSC	Time to First subsequent chemotherapy
TTD	Time to treatment discontinuation

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Truqap
Generic name	Capivasertib
Therapeutic indication as defined by EMA	Truqap is indicated in combination with fulvestrant for the treatment of adult patients with oestrogen receptor (ER)-positive, HER2-negative locally advanced or metastatic breast cancer with one or more *PIK3CA/AKT1/PTEN*-alterations following recurrence or progression on or after an endocrine-based regimen
Marketing authorization holder in Denmark	AstraZeneca AB SE-151 85 Södertälje Sweden
ATC code	L01EX27
Combination therapy and/or co-medication	Combination with fulvestrant
(Expected) Date of EC approval	Positive opinion issued 25.04.2024 and EMA approval was granted 17.06.2024
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	This is the first indication for Truqap
Other indications that have been evaluated by the DMC (yes/no)	No
Joint Nordic assessment (JNHB)	N.A.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	200 mg tablet in 4 x 16 blisters. 160 mg tablet in 4 x 16 blisters Truqap was launched in Medicinpriser.dk October 28th 2024

2. Summary table

Summary	
Indication relevant for the assessment	Capivasertib in combination with fulvestrant for the treatment of adult patients with oestrogen receptor (ER)-positive, HER2-negative locally advanced or metastatic breast cancer with one or more *PIK3CA/AKT1/PTEN*-alterations (´AKT pathway altered´) following recurrence or progression on or after an endocrine-based regimen, who have previously received a CDK4/6 inhibitor (´post CDK4/6i´). **From now on the population relevant for this assessment is called ´AKT pathway altered post CDK4/6i´.**
Dosage regiment and administration	400 mg (2 x 200 mg) oral twice daily (800 mg a day) for 4 days followed by 3 days off treatment. 160 mg strength is available for dose-reductions. Capivasertib should be co-administered with fulvestrant. The recommended dose of fulvestrant is 500 mg administered intramuscular in 28-day cycles on days 1, 15, and once monthly thereafter.
Choice of comparator	Fulvestrant monotherapy
Prognosis with current treatment (comparator)	Main comparator for this assessment and current standard of care treatment in the 2nd line setting in Danish clinical practice is fulvestrant. This is in line with the comparator arm of the Capitello-291 trial. Before moving to 2nd line therapy with fulvestrant, currently, the majority of patients receive an aromatase inhibitor (e.g. letrozole) in combination with a CDK4/6i (palbocilib, ribociclib, abemaciclib) as 1st line therapy according to recommendations in the Danish guidelines. Several recent trials have shown that fulvestrant as monotherapy in 2nd line achieves a median PFS of 2–3 months after progression on a CDK4/6 inhibitor in mBC, warranting the development of better treatment strategies to extend the endocrine treatment window before moving to cytotoxic chemotherapy [1-4]. Moreover, fulvestrant is well tolerated overall, with rare occurrence of grade 3 adverse events (AEs), thus lending itself to be a good combination therapy option [13]. Studies are reporting a mOS of ~25 month in CDK4/6i naïve HR+/HER2- mBC patients [7, 14], however, similar mOS data in a post-CDK4/6i setting for fulvestrant (500 mg) monotherapy are missing. A Danish clinical expert estimated a survival rate of less than 20% at five years for patients in Denmark receiving fulvestrant monotherapy following CDK4/6i [5].
Type of evidence for the clinical evaluation	Head-to-head study, CAPItello-291

Summary	
Most important efficacy endpoints (Difference/gain compared to comparator)	Capivasertib + fulvestrant significantly increased PFS in the AKT pathway altered post CDK4/6i population, with mPFS more than doubled vs. fulvestrant + placebo [redacted] An increase in median OS was observed with capivasertib + fulvestrant vs fulvestrant + placebo [redacted] in the AKT pathway altered post CDK4/6i population.
Most important serious adverse events for the intervention and comparator	In the **capivasertib + fulvestrant** arm, the most commonly occurring AEs of Common Terminology Criteria for Adverse Event (CTCAE) Grade 3 or higher were diarrhoea, rash maculo-papular, rash, anaemia, hypokalaemia, increased AST and hyperglycaemia. No AEs of CTCAE Grade 4 or 5 were reported for diarrhoea, rash maculo-papular, or rash. Three patients had SAEs considered by the investigator as possibly related to **fulvestrant** only: • Injection-site abscess and cerebral infarction in the capivasertib + fulvestrant arm • Platelet count decreased in the placebo + fulvestrant arm.
Impact on health-related quality of life	Clinical documentation: In this assessment, HRQoL outcomes based on the EQ-5D-5L are presented. EQ-5D-5L: • Fulvestrant + placebo: [redacted] • Capivasertib + fulvestrant: [redacted] • Difference: [redacted] Health economic model: Equal HSUV were applied for both treatment arms. • Progression-free: [redacted] • Progressed disease: [redacted] • Difference: [redacted]
Type of economic analysis that is submitted	Type of health economic analysis: Cost-utility analysis Type of model: Partitioned survival model Endpoints: Overall survival, progression-free survival (PFS), time to treatment discontinuation (TTD) and safety
Data sources used to model the clinical effects	CAPItello-291 clinical trial DCO1 and DCO2

Summary	
Data sources used to model the health-related quality of life	CAPItello-291 clinical trial DCO2
Life years gained	0.35 years
QALYs gained	0.28 QALY
Incremental costs	432,790 DKK
ICER (DKK/QALY)	1,540,711 DKK/QALY
Uncertainty associated with the ICER estimate	The parameters with the highest impact on the ICER are HSUV for PFS, discount rate for QALYs, and proportion of patients receiving subsequent treatment following fulvestrant monotherapy
Number of eligible patients in Denmark	Incidence: ~88 patients per year
Budget impact (in year 5)	28,394,414 DKK

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

3.1 The medical condition

Advanced (unresectable or metastatic) breast cancer includes disease that is inoperable or that has spread beyond the axilla to other organs. Despite it being a treatable disease, mBC is considered incurable [6] and has a poor prognosis [7], with metastases being the primary reason of death in patients with BC [8]. While the majority of BCs are diagnosed at an early or locally advanced stage, around 15-20% of those will eventually progress to advanced disease [4, 5, 9], and 2–6% are already metastasized when first detected (*"de novo")* [10].

In both early and advanced disease, treatment and prognosis are guided by disease classification according to hormone receptor (HR) (either progesterone or oestrogen) and human epidermal growth factor receptor 2 (HER2) biomarker status. BC can be divided into following subtypes, HR+/HER2-, HR+/HER2+, HR-/HER2+ and HR-/HER2- (also referred to

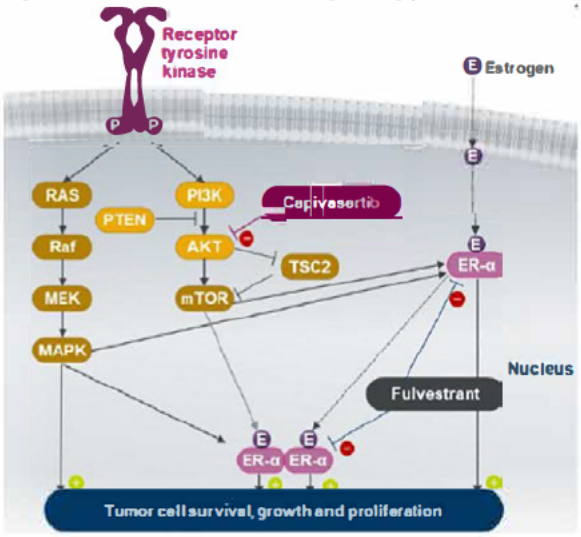
as 'triple negative breast cancer' or 'TNBC') [11]. The HR+/HER2- subgroup relevant to this dossier is the most common subtype, accounting for 70% of all breast cancer cases [12].

Although progress has been made with available treatment regimens for HR+/HER2– mBC in recent decades, survival for patients with stage IV HR+/HER2– BC at 5 years is only 30% [12, 13], with a mean OS (mOS) of 3 years [14]. Therefore, there is still an unmet need for novel treatment options that prolong patient survival, improve HRQoL and control disease burden, specifically in a later line mBC setting.

There are several known genetic and environmental risk factors that can influence the development of BC [15]. Alterations of interest for this application to DMC are those in the AKT pathway (Figure 1). In HR+ BC, AKT pathway hyperactivation occurs in up to 50% of patients, where the majority of deregulation is caused by activating mutations in *PIK3CA*, and to a lesser extent through activating mutations in *AKT1* or through loss-of-function mutations causing low or loss of PTEN protein expression [16-20].

Receptor tyrosine kinase recruits PI3K following activation and phosphorylation, which activates AKT, thereby activating the entire pathway and regulating cell growth.

Figure 1. Schematic of the AKT signalling pathway.



Relevant AKT pathway alterations in HR+/HER2– breast cancer are described in Table 1.

Table 1. AKT pathway alterations in HR+/HER2– breast cancer

Gene (protein)	Alteration	Effect on signalling	References
AKT1	Activating mutation	Hyperactivation of AKT	[17, 21-24]
PIK3CA (p110α/PI3K)	Activating mutation	Hyperactivation of PI3K signalling	[17, 22, 24-31]
PTEN	Loss-of-function mutation or reduced expression	Hyperactivation of PI3K signalling	[24, 25, 29, 32, 33]

HR+ breast cancer patients with alterations in the AKT signalling pathway likely experience rapid disease progression and have worse clinical outcomes [34-37]. Alterations in *PIK3CA*

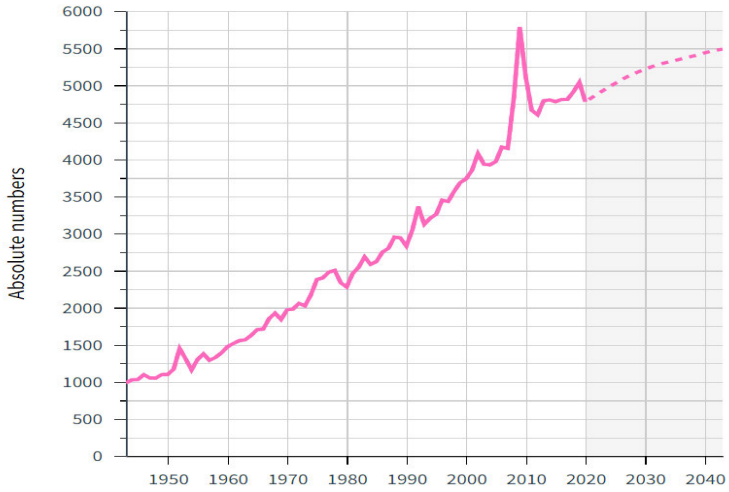
are also associated with a shorter period of time between diagnosis and metastasis compared with breast cancer patients without *PIK3CA* alterations [36], and these alterations are also linked to increased lung metastases [34]. Additionally, HR+/HER2- breast cancer patients with *PIK3CA* and *PTEN* alterations were found to have worse overall PFS and OS compared to patients without these alterations [35, 37]. Furthermore, alterations in AKT signalling may enable malignant cells to become resistant to endocrine treatment (ET) over time [6, 38]. In HR+/HER2– breast cancer, cell proliferation and tumour cell growth are stimulated by oestrogen binding to the ER.[39] Reducing oestrogen levels is therefore a therapeutic target; this can be achieved using ET, which decreases oestrogen production, modulates oestrogen signalling through the ER, and/or antagonizes/degrades the ER [39].

As activation of the AKT pathway is heightened in HR+/HER2– breast cancer, inhibition of this signalling pathway may help overcome resistance to endocrine treatment and provide potential therapeutic strategies for patients with tumours that rely on activation of this signalling pathway [38, 40]. As inhibition of the AKT pathway potentially results in an increase in ER-dependent transcriptional activity, use of an ER antagonist along with AKT inhibition seem as a beneficial treatment strategy for patients with HR+/HER2- breast cancer with aberrant activation of the AKT signalling pathway [41, 42]. Especially in a population where fulvestrant alone only provides 2-3 months in PFS [1, 2, 43, 44].

3.2 Patient population

The prevalence of breast cancer cases in 2022 was around 77.000 for women [45, 46] and around 430 for men in Denmark [45]. Breast cancer incidence for men and women across all ages was 4.981 in 2021 and increased to 5.085 in 2022 [47] with predictions indicating further increases in new breast cancer cases every year according to Nordcan (Figure 2).

Figure 2. Incidence of breast cancer (women) and future trend



***Source**: Nordcan [48]*

Incidences and prevalences for the past years based on a 2024 data report from the Danish Cancer registry are described in Table 2.

Table 2. Incidence and prevalence (in women) in the past 5 years

Year	2018	2019	2020	2021	2022	2023
Incidence in Denmark per 100.000*	146,7	149,3	139,7	143,3	145,0	149,9
Prevalence in Denmark*	70 238	72 263	73 976	75 645	77 263	79 086
Global prevalence **	N/A	N/A	N/A	N/A	N/A	N/A
Prevalence of HR-positive mBC***	7375	7588	7767	7943	8113	8304

*Note: * Age-standardized incidence rate (to the age composition of the Danish population in 2000) (per 100,000 women) and prevalence of breast cancer in women based on annual rapport from cancer registry [46]** Global Cancer Observatory: Cancer Today (version 1.1), 2024 [49] *** Prevalence HR-positive breast cancer assumed to be equal to ~70% annual prevalence[12]. Those eventually developing metastatic disease to estimate to 15% [4] [5]*

The target population of this application is addressing 2nd line patients that have received CDK4/6 inhibitors in combination with endocrine therapy as the 1st line standard of care, according to Danish treatment guidelines. Further, those patients would be eligible for continued therapy with endocrine treatment and carry mutations in any of the *PIK3CA/AKT1/PTEN* genes. Restricting the target population on this sub-group of the clinical trial ("AKT pathway altered 2nd line HR+ HER2- mBC patients that have received prior CDK4/6i") is in line with recent DMC general statements of emphasizing the prioritization of subgroups of the trial which are clinically of highest relevance compared to the overall trial population. Further this sub-population is aligned with the Danish real-world praxis where only patients who have previously received CDK4/6 inhibitors would be eligible for capivasertib and endocrine treatment or another endocrine treatment in monotherapy, *i.e.* fulvestrant. Finally, there is still an unmet need for novel treatment options that prolong patient survival, improve HRQoL and control disease burden, specifically in this a later line mBC setting.

Estimated numbers of patients eligible for treatment are depicted in Table 3.

Table 3. Patient funnel for the indication in scope

Overview of patient funnel calculation	Patient incidence
In 2026, the estimated incidence of breast cancer in females in Denmark will be 5216 patients [48]	~5216 incident breast cancer patients in 2026
Up to 70% [12] [5] will be of the HR+/HER2-negative subgroup.	~3651 new pts yearly with HR+/HER2- BC
Of those, ~15% [4] [5] are expected to develop inoperable locally advanced or metastatic breast cancer within 10 years.	~548 pts with HR+/HER2- mBC

Clinical experts approximate that the majority, ~80%, of patients would currently receive CDK4/6 inhibitors in combination with ET in this setting [5].	~438 pts receiving 1st line treatment with CDK4/6 inhibitors + ET
Further 80% of patients progressing on 1st line would be eligible for continued therapy [5].	~351 patients receiving any 2nd line treatment
Approximately 50% of the 2nd line treated patients will be eligible for continued ET [5].	~175 patients thereof considered for continued ET
According to trial data, up to 50% of HR+ HER2- mBC patients are carrying mutations in the *PIK3CA/AKT1/PTEN* genes [16-19].	~88 patients thereof with alterations in the AKT pathway

Estimated numbers of patients eligible for treatment in the upcoming years are depicted in Table 4.

Table 4. Estimated number of patients eligible for treatment

Year	2026	2027	2028	2029	2030
Number of patients in Denmark who are eligible for treatment in the coming years	88	88	89	89	90

Note: Based in yearly incline in the estimated absolute numbers of incidence of breast cancer in females in Denmark according to NordCan predictions [48].

3.3 Current treatment options

According to Danish guidelines [4], ET (typically an AI) is recommended in combination with a CDK4/6i in the 1st -line setting of HR+ HER2-negative BC patients. There may be exemptions where the patient first receives this combination in the 2nd line [50], or is either not eligible for this combination or declines the therapy [4].

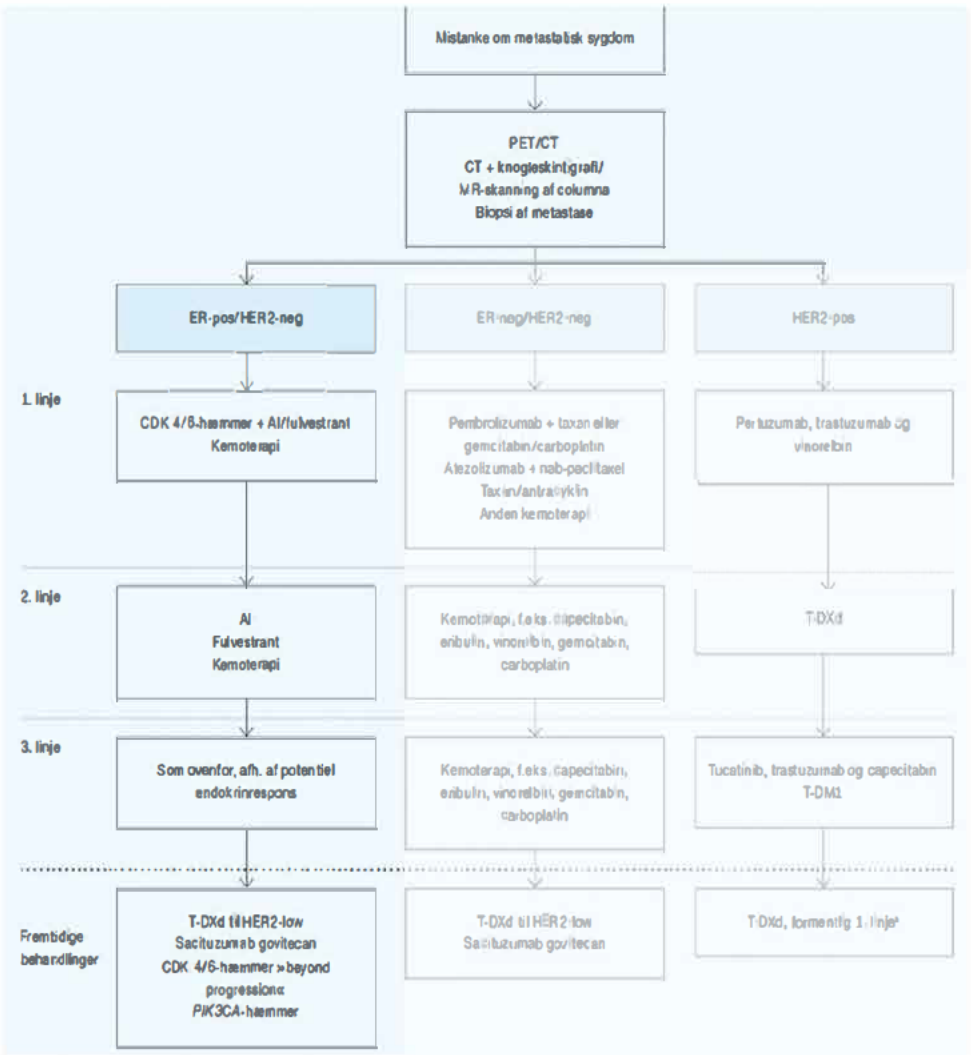
According to Danish Real-world data [50], 1st-line median OS on CDK4/6 inhibitors was around 37.8- 54.4 months.

In case of progression on a CDK4/6i in combination with an AI, there are few possible consecutive treatment alternatives [4]. Individual assessments are taken to determine the choice of following treatment considering time to progress, tumor burden, performance status, comorbidity and patient preference. Specifically, patients who experience early progression (*i.e.* less than 6 months after starting CDK4/6i treatment) are considered to have developed primary endocrine resistance and are therefore not expected to benefit from further ET. These patients are offered chemotherapy instead.

Nevertheless, the majority of patients experience progression later than 6 months after starting the treatment and are thus presumed to be able to benefit from further ET. Fulvestrant is the most frequently used ET after treatment with a CDK4/6i combined with an AI [5], however, as described earlier, expected prognoses in this setting are poor, with 2-3 months in PFS [1, 2, 4, 44]. Thus, despite of the considerable overall survival seen with

1st-line treatment, the current 2nd-line options are very limited and hence there is a need for an alternative 2nd-line treatment that can improve the PFS.

Figure 3. Flowchart of treatment choices for metastatic breast cancer [51]



3.4 The intervention

An overview of capivasertib, according to the indication is provided in Table 5.

Table 5. Overview of capivasertib

Overview of intervention	
Indication relevant for the assessment	Capivasertib in combination with fulvestrant for the treatment of adult patients with oestrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer with one or more *PIK3CA/AKT1/PTEN*-alterations ('AKT pathway altered') following recurrence or progression on or after an

Overview of intervention	
	endocrine-based regimen, who have previously received a CDK4/6 inhibitor ('post CDK4/6')
ATMP	N.A.
Method of administration	Tablet for oral use
Dosing	Capivasertib tablets (used in combination with fulvestrant) are administered at a recommended dose of 400 mg (two 200 mg tablets), taken orally twice daily (approximately 12 hours apart) with or without food, for 4 days followed by 3 days off-treatment.
Dosing in the health economic model (including relative dose intensity)	The dosing in the health economic model is in line with the recommended dosing of capivasertib + fulvestrant as presented above. In the health economic analysis dose reductions, and not RDI per se, were accounted for. Given that there is no difference in price between 200mg and 160mg packages of Truqap, only two dose reductions have an impact on the acquisition costs (i.e. same price for 160mg and 200mg strength packages of 64 tablets). Data on dose reductions was not available for the AKT pathway altered post CDK4/6i patient cohort. [redacted] (see section 11.1 regarding dose reductions in CAPItello-291 trial). [redacted]
Should the medicine be administered with other medicines?	In combination with fulvestrant.
Treatment duration / criteria for end of treatment	Treatment with capivasertib should continue until disease progression or occurrence of unacceptable toxicity. Treatment may be interrupted to manage adverse reactions and dose reductions may be considered.
Necessary monitoring, both during administration and during the treatment period	Patients must be tested for fasting blood glucose levels and HbA1C prior to start of treatment with capivasertib and monitored at specific intervals. Fasting glucose levels should be monitored at weeks 1, 2, 4, 6 and 8 after treatment start and monthly thereafter, additionally, it is recommended to test

Overview of intervention	
	fasting blood glucose levels pre-dose at Day 3 or 4 of the dosing week. HbA1c should be monitored every 3 months after initiating treatment with capivasertib. Additional monitoring costs are included in the health economic model (see section 11.4).
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	Danish clinical practice does not routinely examine patients for either *PIK3CA, AKT1 or PTEN* mutation. However, the *PIK3CA* mutation can be detected by using e.g. next generation sequencing (NGS) which is a laboratory technique implemented at the hospitals in Denmark. The Danish pathology departments have updated the national pathology guideline to include *PIK3CA* analysis [52]. Testing for identifying AKT alterations is included in the economic model as a one-off cost (see section 11.8).
Package size(s)	200 mg tablet in 4 x 16 blisters. 160 mg tablet in 4 x 16 blisters Truqap was launched in Medicinpriser.dk October 28th 2024

3.4.1 Description of ATMP

N.A.

3.4.2 The intervention in relation to Danish clinical practice

Capivasertib will be used in combination with fulvestrant to treat patients with unresectable or metastatic HR+/HER2– breast cancer whose disease has recurred or progressed following treatment with an endocrine therapy-based regimen in combination with a CDK4/6i.

In the CAPItello-291 trial, fulvestrant monotherapy is the comparator arm in this 2nd line setting, which is in line with current Danish clinical practice and guidelines, when patient still show to have sensitivity to an ET.

This assessment focusses only on the sub-population of the Capitello-291 trial with patients who have previously received CDK4/6i in combination with an AI (e.g. letrozole) in 1st line. This sub-population (70% of the trial population) is aligned with the Danish real-world praxis where only patients who have previously received CDK4/6i would be eligible for capivasertib and ET or another ET in monotherapy, *i.e.* fulvestrant.

One may discuss that for patients who have endocrine sensitive disease (progression > 12 months after completing adjuvant endocrine therapy), either an AI or fulvestrant as ET-partner to a CDK4/6i is reasonable, given the similar efficacy in the PARSIFAL study [53].

However, an AI is preferred in Danish clinical practice due to oral administration and more data exist for fulvestrant post progression on an AI [54-57].

When ET options are exhausted for HR+ patients, one may choose chemotherapy after progression on endocrine treatments and/or preferred CDK4/6 inhibitor according to Danish guidelines. This will however depend on tumour burden and comorbidities etc. [4].

3.5 Choice of comparator(s)

The choice of comparator for this submission is fulvestrant (Table 6). As described above, fulvestrant monotherapy is according to current Danish clinical practice and guidelines [4], the only therapy option in the 2nd-line setting, when patient still show to have sensitivity to an endocrine treatment after progress on aromatase inhibitors in combination with CDK4/6 inhibitors.

Most patients will have received an aromatase inhibitor (e.g. letrozole) in 1st- line combined with a CDK4/6 inhibitor. Hence, fulvestrant is the most frequently used endocrine treatment following progression on a CDK4/6 inhibitor in combination with an aromatase inhibitor.

Table 6. Overview of fulvestrant

Overview of fulvestrant	
Generic name	Fulvestrant
ATC code	L02BA03
Mechanism of action	Fulvestrant is a competitive ER antagonist with an affinity comparable to estradiol. Fulvestrant blocks the trophic actions of estrogens without any partial agonist (estrogen-like activity). The mechanism of action is associated with down-regulation of estrogen receptor protein levels.
Method of administration	Intramuscular injections.
Dosing	500 mg (2 injections) on Day 1 of Weeks 1 and 3 of cycle 1, and then on Day 1, Week 1 of each cycle thereafter
Dosing in the health economic model (including relative dose intensity)	The median (interquartile range; IQR) percentage of the actual dose delivered relative to the intended dose (i.e., the relative dose intensity) [redacted] for fulvestrant in both treatment groups (overall population). The exposures and relative dose intensities in the altered subgroup SAS were similar to those of the overall population SAS.
Should the medicine be administered with other medicines?	Not for the patient population in scope for this application.

Overview of fulvestrant	
Treatment duration/ criteria for end of treatment	To progression.
Need for diagnostics or other tests (i.e. companion diagnostics)	HR and estrogen positive.
Package size(s)	Pack containing 2 glass pre-filled syringes. Safety needles (BD SafetyGlide) for connection to each barrel are also provided.

3.6 Cost-effectiveness of the comparator(s)

Fulvestrant has been on the market for many years and has not been assessed by DMC. Further the product is not labelled as a hospital product and therefore a supplementary analysis is not included in this application. Finally, given that fulvestrant is generic it is very likely that it would show to be cost-effective if evaluated.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Table 7. Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
PFS in the AKT altered post CDK4/6i population [Capitello-291]	DCO1 (15 Aug 2022) Median FU: [redacted] and [redacted] for capivasertib+fulv and fulvestrant, respectively.	PFS was defined as the time from the date of randomization until the date of objective disease progression, as defined by Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria, or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomized therapy or receives another anti-cancer therapy prior to progression.	PFS was assessed by an investigator, and a sensitivity analysis of PFS assessed by blinded independent central review (BICR) was performed.
OS in the AKT altered post CDK4/6i population [Capitello-291]	DCO2 (15 April 2024) [redacted]	OS is the length of time from randomization until	

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
	[redacted]	the date of death due to any cause.	
PFS2 in the AKT altered post CDK4/6i population [Capitello-291]	DCO2 (15 April 2024)	The time from randomization until second progression on next-line treatment, as assessed by the investigator at the local site, or death due to any cause.	
Safety and tolerability in the Safety Analysis Set (SAS) [Capitello-291]	DCO2 (15 April 2024)	Evaluated in terms of AEs/SAEs, vital signs, clinical chemistry/haematology/glucose metabolism parameters and ECG parameters.	
HRQoL [Capitello-291]	DCO2 (15 April 2024)	Evaluation of EORTC QLQ-C30, EORTC QLQ-BR23, scale/item score, including change from baseline and time to deterioration.	

* Time point for data collection used in analysis (follow up time for time-to-event measures)

Validity of outcomes

OS and PFS are well established endpoints within oncology and mBC.

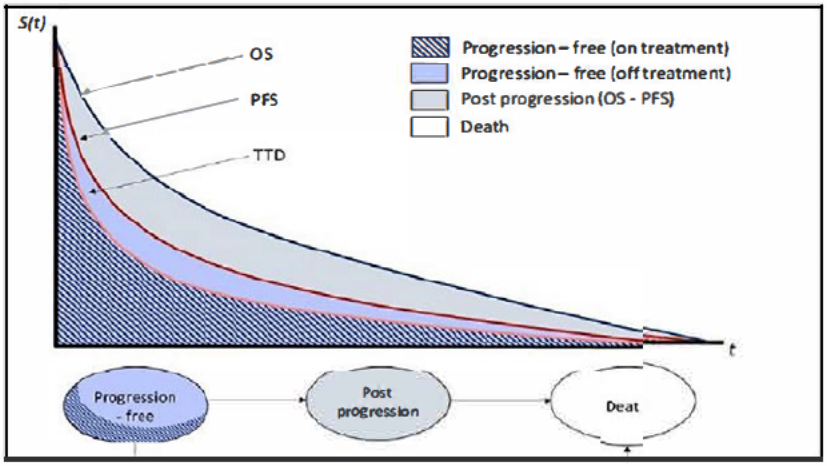
4. Health economic analysis

4.1 Model structure

A three-state cohort-based partitioned survival model (PSM) with health states for progression-free (PF), progressed disease (PD), and death was developed in Excel®. PSMs are ideal for irregular event intervals or censoring by relying on PFS and OS data directly at each time point, rather than explicit transition probabilities. Directly modelling time-to-event data from trials improves the internal validity of cost-effectiveness analysis,

supporting the use of PSMs. The PSM approach is consistent with the approaches accepted in previous appraisals in mBC in Denmark [58-60]. A schematic of the model state structure is presented in Figure 4 below.

Figure 4. Schematic of the model structure



The three health states are defined as follows:

- **Progression-free (PF)**: patients are free of disease progression
- **Progressed disease (PD)**: patients have radiologically confirmed progressed disease
- **Death**: Absorbing state for deaths from any cause

These health states are mutually exclusive and exhaustive, meaning each patient occupies only one state at any time. They reflect the key sequence of events during mBC treatment, including progressive disease onset, which requires a treatment change, incurring costs and worsening HRQoL. Health state occupancy is based on CAPItello-291 clinical trial data. OS is divided into PF and PD states using the PFS curve, with PF derived from PFS cumulative survival probabilities, PD from OS minus PFS, and death from one minus OS (Figure 4). PFS is constrained to not exceed OS to prevent negative state membership, and the death hazard is constrained to not go below background mortality rates to avoid exceeding general population survival [61]. The analysis uses a 20-year time horizon to represent a patient's lifetime, with no changes in costs and QALYs expected thereafter. OS and PFS are extrapolated beyond CAPItello-291 follow-up using parametric survival functions, with further details in Appendix D.

4.2 Model features

A description of the model and settings of the analysis are presented in Table 8.

Table 8. Features of the economic model

Model features	Description	Justification
Patient population	HR+ HER2-mBC with one or more PIK3CA/AKT1/PTEN-	In Denmark, the combination treatment with CDK4/6i + endocrine treatment has emerged as the foremost frontline therapeutic option for patients

Model features	Description	Justification
	alterations following treatment with CDK4/6i	with HR+/HER2- mBC. The fraction of patients not receiving CDK4/6i in the 1L setting, usually due to fragility, may not be eligible for combination therapy, including capivasertib + fulvestrant in the 2L setting either. Therefore, capivasertib + fulvestrant is expected to be used only for HR+/HER2- mBC patients with AKT pathway alterations who have previously received CDK4/6i.
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Lifetime (20 years)	To capture all health benefits and costs in line with DMC guidelines. Based on mean age at diagnosis in the clinical trial population (mean 57.7 years).
Cycle length	1 month (30.44 days)	This was considered the shortest time period in which a change in the disease course or symptoms would be observed in clinical practice.
Half-cycle correction	Yes	Used to improve the accuracy of health economic models by adjusting for the assumption that events occur halfway through each cycle, providing more precise estimates of costs and outcomes.
Discount rate	3.5 %	In line with the guidelines by DMC [62]
Intervention	Capivasertib (Truqap) in combination with fulvestrant	
Comparator(s)	Fulvestrant monotherapy	The most relevant treatment option for patients who are eligible for an ET-based regimen following the treatment with CDK4/6i according to the national treatment guidelines [4].
Outcomes	OS, PFS, TTD, HRQoL, safety	Primary endpoints in CAPItello-291 trial and relevant to reflect the disease

5. Overview of literature

The application is based on the head-to-head study vs. fulvestrant (CAPItello-291). Fulvestrant is believed to be a relevant comparator in Danish clinical practice as detailed in section 3.5. No analysis inputs based on a systematic literature review were therefore used.

5.1 Literature used for the clinical assessment

Table 9. 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*
Capivasertib in Hormone Receptor–Positive Advanced Breast Cancer. Nicholas C. Turner, M.D. et al. N Engl J Med 2023;388:2058-2070 DOI: 10.1056/NEJMoa2214131.VOL. 388 NO. 22. [63]	CAPItello-291	NCT04305496	Start: June 2, 2020 Data cut-off date (DCO1): August 15, 2022 Data cut-offs not included in the publication: DCO2: April 15, 2024 (data on file) DCO3 is planned	Capivasertib + fulvestrant vs fulvestrant

* If there are several publications connected to a trial, include all publications used.

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

The literature used for the assessment of HRQoL is presented in Table 10.

Table 10. Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference numr)	Health state/Disutility	Reference to where in the application the data is described/applied
Capivasertib in Hormone Receptor–Positive Advanced Breast Cancer. Nicholas C. Turner, M.D. et al. N Engl J Med 2023;388:2058-2070 DOI: 10.1056/NEJMoa2214131.VOL. 388 NO. 22. [63]	Health state utility	See section 10.2.3

Reference (Full citation incl. reference numr)	Health state/Disutility	Reference to where in the application the data is described/applied
Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes. 2008 Oct 21;6:84. doi: 10.1186/1477-7525-6-84. PMID: 18939982; PMCID: PMC2579282. [64] Diarrhoea, rash Table 2. Results of the mixed model analysis	Disutility	See section 10.2.3
Smith-Palmer J, Bae JP, Boye KS, Norrbacka K, Hunt B, Valentine WJ. Evaluating health-related quality of life in type 1 diabetes: a systematic literature review of utilities for adults with type 1 diabetes. Clinicoecon Outcomes Res. 2016 Oct 7;8:559-571. doi: 10.2147/CEOR.S114699. PMID: 27785079; PMCID: PMC5063604. [65] Hyperglycaemia Table 1. EQ-5D-3L health state utility/disutility values for diabetes-related complications in patients with type 1 diabetes	Disutility	See section 10.2.3
Bounthavong M, Butler J, Dolan CM, Dunn JD, Fisher KA, Oestreicher N, Pitt B, Hauptman PJ, Veenstra DL. Cost-Effectiveness Analysis of Patiromer and Spironolactone Therapy in Heart Failure Patients with Hyperkalemia. Pharmacoeconomics. 2018 Dec;36(12):1463-1473. doi: 10.1007/s40273-018-0709-3. Erratum in: Pharmacoeconomics. 2019 Aug;37(8):1071. doi: 10.1007/s40273-019-00809-1. PMID: 30194623; PMCID: PMC6244629. [66] Hypokalaemia 1-Month disutility associated with hospitalization Table 1. Parameters used in the cost-efectiveness analysis	Disutility	See section 10.2.3
NICE (2019). "Abemaciclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer." from https://www.nice.org.uk/guidance/ta563. [67] Anaemia	Disutility	See section 10.2.3

Reference (Full citation incl. reference numr)	Health state/Disutility	Reference to where in the application the data is described/applied
Table 30. Adverse event disutilities Swinburn P, Lloyd A, Nathan P, Choueiri TK, Cella D, Neary MP. Elicitation of health state utilities in metastatic renal cell carcinoma. Curr Med Res Opin. 2010 May;26(5):1091-6. doi: 10.1185/03007991003712258. PMID: 20225993. [68] Stable with no AE (0.795) – Stable with aneamia grade III (0.676) = disutility linked to anemia (0.119) Table 1. Elicitation of health state utilities in metastatic renal cell carcinoma		
Lloyd, A., Nafees, B., Narewska, J. et al. Health state utilities for metastatic breast cancer. Br J Cancer 95, 683–690 (2006). https://doi.org/10.1038/sj.bjc.6603326 [69] Stomatitis Table 3. Utility value of base state (stable MBC on treatment with no toxicity) and utility gains and decrements associated with departures from this health state	Disutility	See section 10.2.3

5.3 Literature used for inputs for the health economic model

Literature used for the health economic model are presented in Table 11.

Table 11. 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
Capivasertib in Hormone Receptor–Positive Advanced Breast Cancer. Nicholas C. Turner, M.D. et al. N Engl J Med 2023;388:2058-2070 DOI: 10.1056/NEJMoa2214131.VOL. 388 NO. 22. [63] *Data on file (specifically for the post CDK4/6i population and DCO2)	OS * PFS * TTD * Adverse events * Proportion of patients that received a 2nd dose reduction * Patient characteristics *	Pivotal trial	See sections 6,8, 9 and 11.1
EMA. "SUMMARY OF PRODUCT CHARACTERISTICS - Faslodex." from https://ec.europa.eu/health/documents/community-register/2020/20201027149621/anx_149621_en.pdf. [70]	Dosing - Fulvestrant	Targeted literature search	See section 11.1
EMA. "SUMMARY OF PRODUCT CHARACTERISTICS - Capecitabine." from https://www.ema.europa.eu/en/documents/product-information/xeloda-epar-product-information_en.pdf. [71] EMA. "SUMMARY OF PRODUCT CHARACTERISTICS - Eribulin." from https://ec.europa.eu/health/documents/community-register/2016/20160816135473/anx_135473_en.pdf. [72] EMA. "SUMMARY OF PRODUCT CHARACTERISTICS - Paclitaxel." from https://www.ema.europa.eu/en/documents/product-information/abraxane-epar-product-information_en.pdf. [73]	Dosing – Subsequent treatments	Targeted literature search	See section 11.6

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Round J, Jones L, Morris S. Estimating the cost of caring for people with cancer at the end of life: A modelling study. Palliat Med. 2015 Dec;29(10):899-907. doi: 10.1177/0269216315595203. Epub 2015 Jul 21. PMID: 26199134; PMCID: PMC4669033. [74]	Terminal care costs	Targeted literature search	See section 11.8
DRG 2025 [75]	Disease management costs – Unit costs IM administration cost Adverse events management costs	Targeted literature search	See section 11
See Table 10	Health state utility & Disutilities	Targeted literature search	See section 10.2.3

6. Efficacy

6.1 Efficacy of capivasertib + fulvestrant compared to placebo + fulvestrant for 2L+ HR+ HER2- Breast Cancer

6.1.1 Relevant studies

The only study relevant to document the effect and safety of capivasertib in combination with fulvestrant compared to fulvestrant monotherapy in 2L+ HR+ HER2- metastatic breast cancer is Capitello-291. An overview of the study design is given in Table 12. Patients in the study must have had a relapse or disease progression during or after treatment with an AI, with or without previous CDK4/6i therapy. The dual primary end point was investigator-assessed progression-free survival assessed both in the overall population and among patients with AKT pathway altered (*PIK3CA, AKT1, or PTEN*) tumours. Of all patients included in the study, 48% had alterations in the AKT pathway and 69.1% had previously received a CDK4/6i [63].

The populations in scope for this application is a subpopulation of the study*, i.e.* patients that carry alterations in the AKT pathway (dual primary and key secondary endpoints) and that have earlier received CDK4/6i (stratification factor). Whereas analyses for the subpopulation (AKT pathway altered) was a prespecified primary and secondary endpoint, analyses of the ITT post CDK4/6i stratification separately [76] or the AKT pathway altered population post CDK4/6i stratification were exploratory subgroup analyses, and not prespecified in the study protocol/statistical plan.

Also the FAKTION trial [77], an externally sponsored, randomised, multicentre, double-blind, placebo-controlled, phase II trial, assessed capivasertib + fulvestrant as a treatment for HR+/HER2- mBC, who had relapsed or progressed on an AI. However, in contrast to CAPItello-291, most patients were not exposed to CDK4/6i prior to the trial.

Table 12. 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 time
CAPItello-291 NCT04305496	Randomized phase III / open-label / placebo-control/ active comparator-control. 1:1 ratio	28 month (first participant enrolled to first primary analysis) [78]	Overall population, (intention-to-treat population) including all patients with ET-resistant HR+/HER2– locally advanced (inoperable) or metastatic breast cancer Altered population, including those patients with ET-resistant HR+/HER2– locally advanced (inoperable) or metastatic breast cancer and known genetic alterations in *PIK3CA*, *AKT1* or *PTEN*	400 mg bid (2 tablets of 200 mg taken bid; total daily dose 800 mg) given on an intermittent weekly dosing schedule. Patients were dosed on Days 1--4 in each week of a 28-day treatment cycle	Fulvestrant. 500 mg (2 injections) on Day 1 of Weeks 1 and 3 of cycle 1, and then on Day 1, Week 1 of each cycle thereafter	**Dual primary endpoints:** PFS by investigator assessment, overall or in AKT pathway altered tumors (≥1 qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration) **Secondary endpoints**: OS, PFS2, ORR, Duration and onset of response, Clinical benefit rate, Safety and tolerability, HRQoL for both ITT and AKT pathway altered populations **Exploratory endpoints**: Patient-reported tolerability, Time to first subsequent chemotherapy or death, Healthcare resource use and Impact of treatment and disease state on health state utility. The **median FU time** for the AKT pathway altered post CDK4/6i subgroup by endpoint and by arm (capivasertib+fulv and fulvestrant respectively) is: [redacted]

6.1.2 Comparability of studies

Not applicable

6.1.2.1 Comparability of patients across studies

Not applicable

Table 13. Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety – N/A

	[Study name]		[Study name]		[Study name]	
	[int./ comp.]	[int./ comp.]	[int./ comp.]	[int./ comp.]	[int./ comp.]	[int./ comp.]
Age	N/A	N/A	N/A	N/A	N/A	N/A
Gender	N/A	N/A	N/A	N/A	N/A	N/A

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

In Table 14, characteristics in the relevant Danish population are described alongside those used in the health economic model. Patient characteristics were discussed and validated by a clinical expert [5].

Table 14. Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population [5]	Value used in health economic model (reference if relevant)
Age	67 - 69†	57.7* (mean age)
Gender: Female	99%	99%*
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

*Based on AKT pathway altered post CDK4/6i population from the CAPItello-291 trial [63] †Based on clinical expert opinion and Danish RWE – the age of 69 years was explored in a scenario analysis (see Appendix K) ‡Estimated based on mean weight and mean height [redacted] of the AKT pathway altered post CDK4/6i population from the CAPItello-291 trial

Figure 5 shows OS KM curves for two distinct patient populations:

- Dotted black line: AKT pathway altered post CDK4/6i patients who received placebo plus fulvestrant in the CAPItello-291 trial (mean age 57.7 years)

- Solid gray line: Patients who received fulvestrant monotherapy as 2L treatment for mBC after 1L CDK4/6i in Denmark (mean age 69 years) (see Appendix K)

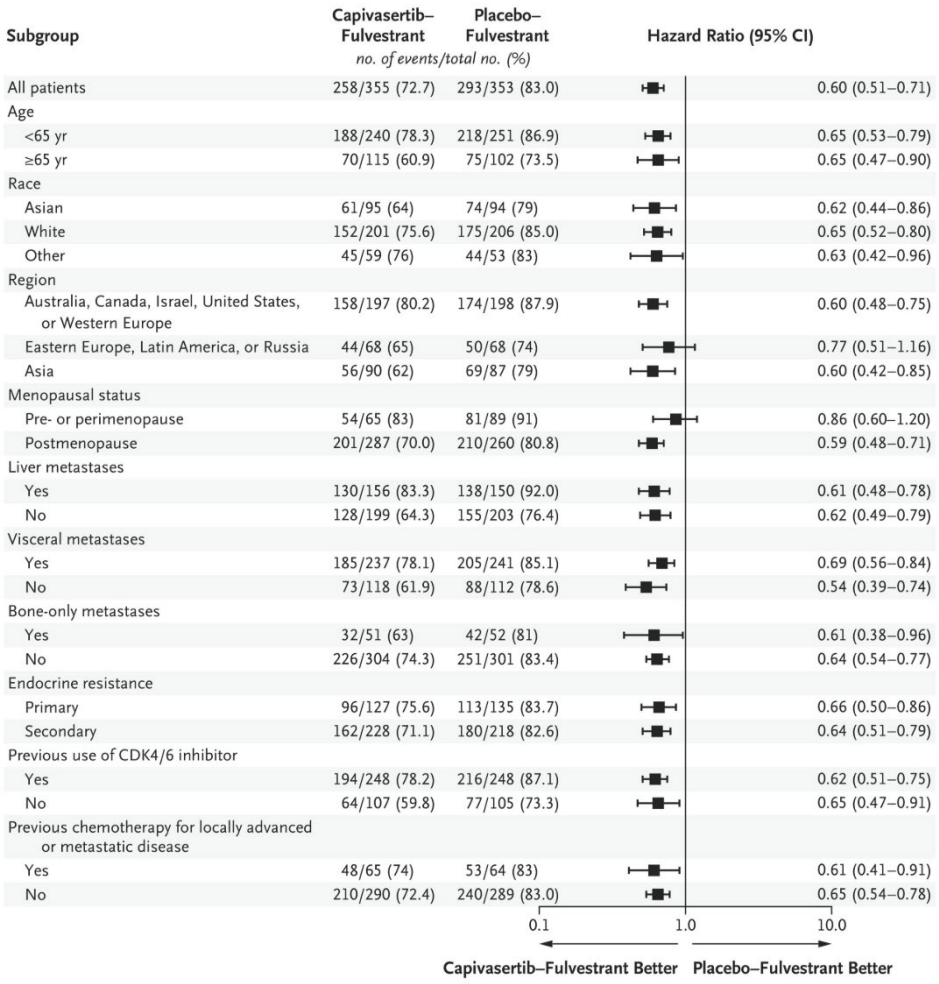
The two OS KM curves in Figure 5 demonstrate similar trends and overall alignment. Despite the notable difference in age demographics, with the Danish patient population being generally older than the clinical trial participants (mean age: 69 years for the real-world fulvestrant patients in Denmark vs. 57.7 years for AKT pathway altered post CDK4/6i patients in CAPItello-291), the curves suggest comparable OS outcomes between the two groups. This implies that the efficacy of fulvestrant-based treatment in second line may be consistent across different age groups and geographical settings. Notably, age was not identified as a treatment effect modifier in the CAPItello-291 study assessing the PFS of the overall study population (Figure 6) [63]. It is assumed that this also applies to patients with AKT pathway alterations in the post CDK4/6i setting.

The comparable performance between the clinical trial population and the real-world Danish patients suggests a high degree of external validity for the CAPItello-291 trial results, despite potential age differences between the two cohorts.

Given that age was not found to be a treatment effect modifier in the CAPItello-291 trial [63], it can be reasonably concluded that the efficacy results observed for the combination of capivasertib and fulvestrant are likely to be applicable to the Danish patient population as well.

Figure 5. Overall survival for the placebo + fulvestrant arm of the CAPItello-291 trial and patients that received fulvestrant in 2L in Denmark

Figure 6. Subgroup analysis of investigator-assessed PFS in the overall population [63]



6.1.4 Efficacy – results per CAPItello-291

6.1.4.1 DCOs

The data cut-off (DCO) date for the primary analysis of PFS was 15 August 2022 (DCO1), approximately 12 months after the last patient was randomized. Primary analysis took place once PFS data had reached 77% maturity in the AKT pathway altered population. In total, 708 patients were randomized to receive treatment with capivasertib + fulvestrant (n=355) or placebo + fulvestrant (n=353). Three patients in the placebo + fulvestrant group did not receive treatment; one died before their first dose, one withdrew consent, and the reason for the remaining patient was unknown.

The latest CAPItello-291 data cut-off (DCO2, April 2024) was a pre-specified events-driven data cut-off for the interim analysis of OS in the study protocol and statistical analysis plan (SAP) and was part of a post-regulatory commitment. In addition to OS, other endpoints such as PFS2, time to first subsequent chemotherapy (TFSC), safety and tolerability, and patient-reported outcomes (PROs) were updated. PFS was not updated as the primary and final PFS analysis was based on DCO1. The post CDK4/6i subgroup analysis of the AKT

pathway altered population (i.e., AKT pathway altered post CDK4/6i subgroup analysis) has not been included in the regulatory processes and is consequently not publicly available.

Results

Efficacy results from the CAPItello-291 trial were analysed separately for the overall study population and the sub-population with alterations in *PIK3CA/AKT1/PTEN* (the altered population).

6.1.4.2 PFS (DCO1)

PFS was defined as the time from the date of randomization until the date of objective disease progression, as defined by Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria, or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomized therapy or receives another anti-cancer therapy prior to progression. PFS was assessed by an investigator, and a sensitivity analysis of PFS assessed by blinded.

At the time of DCO1, there were [redacted] PFS events [redacted]) among the patients who had received CDK4/6i treatment prior to the CAPItello-291 trial (i.e., AKT pathway altered post CDK4/6i population), with more events observed in the placebo + fulvestrant arm than the capivasertib + fulvestrant arm [redacted] which is in line with the label population. The median PFS was [redacted] months for patients in the placebo + fulvestrant arm versus [redacted] for patients in the capivasertib + fulvestrant arm (Table 15). The difference in PFS between the two-treatment arms was statistically significant. The HR was [redacted]

Table 15. PFS from the CAPItello-291 trial for patients with AKT pathway altered post CDK4/6i population, DCO1

Treatment arm	N	Events	Maturity	RMST* PFS – months (95% CI)	Median PFS – months (95% CI)
Capivasertib + fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo + fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*** The RMST calculation uses a cut-off value of 19.5 months. This is the smallest value among the largest observed times across the treatment groups.**

The KM plot for PFS is shown in Figure 7 below and shows a clear, rapid, and continued separation between the two arms over time. The survival rates at 12, 24, and 36 months for PFS is shown in Table 16.

Figure 7. CAPItello-291 PFS KM curves (AKT pathway altered post CDK4/6i population, DCO1)

Table 16. PFS survival rates from the CAPItello-291 trial for patients with AKT pathway altered post CDK4/6i population, DCO1

At time point	Capivasertib + fulvestrant	Placebo + fulvestrant
12 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]

Abbreviation: N/A: not available
Note: The latest time point captured in the PFS KM curves is [redacted] months with PFS survival rates equal to [redacted] for the capivasertib + fulvestrant and placebo + fulvestrant arms respectively
Source: data on file; CEM

6.1.4.3 Overall survival (DCO2)

At DCO2, median OS for the AKT pathway altered post CDK4/6i population was 21.2 months for the placebo + fulvestrant arm [redacted] for the capivasertib+fulvestrant arm [redacted]). The hazard ratio (HR) for the AKT pathway altered post CDK4/6i patient population is [redacted] (Table 17). The Kaplan-Meier (KM) curves are presented in Figure 8. The survival rates at 12, 24, and 36 months for OS is shown in Table 18.

Table 17. OS estimates from the CAPItello-291 trial DCO2 (capivasertib + fulvestrant and placebo + fulvestrant) (AKT pathway altered post CDK4/6i)

Arm	N	Events	Maturity	Median, months (95% CI)	Hazard ratio (95% CI)

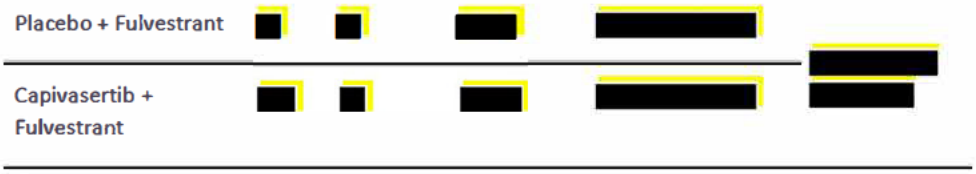


Figure 8. CAPItello-291 DCO2 OS KM curves (AKT pathway altered post CDK4/6i)

Based on the

Table 18. OS survival rates from the CAPItello-291 trial for patients with AKT pathway altered post CDK4/6i population, DCO1

At time point	Capivasertib + fulvestrant	Placebo + fulvestrant
12 months		
24 months		
36 months		

Source: data on file; CEM

6.1.4.4 Second progression-free survival (DCO2)

Treatment of HR+/HER2– mBC with anti-cancer agents may affect the drug resistance profile of the target tumour(s), which may impact on the activity of next-line therapies.[79]

For this reason, PFS2 was measured to ascertain the effect of treatment with capivasertib + fulvestrant on patients' survival following treatment with a subsequent regimen. At the time of DCO2, PFS2 data from CAPItello-291 were approximately [redacted] for capivasertib + fulvestrant and [redacted] for placebo + fulvestrant.

In the AKT pathway altered post CDK4/6i population, treatment with capivasertib + fulvestrant conferred a [redacted] reduction in the risk of a second progression compared with placebo + fulvestrant [redacted]. Median PFS2 was [redacted] for patients in the capivasertib + fulvestrant arm compared with that for patients in the placebo + fulvestrant arm [redacted] (Table 19).

Table 19. Investigator-assessed PFS2 in AKT pathway altered post CDK4/6i population (DCO2)

	AKT pathway altered post CDK4/6i population	
	Capivasertib + fulvestrant [redacted]	**Placebo + fulvestrant** [redacted]
Total number of patients with events, n (%)*	[redacted]	[redacted]
Median PFS2 (months)†	[redacted]	[redacted]
95% CI for median PFS2†	[redacted]	[redacted]
Hazard ratio§	[redacted]	
95% CI for hazard ratio§	[redacted]	
Median (range) duration of follow-up in censored patients (months)	[redacted]	[redacted]

Notes: **Progression events determined by investigator assessment subsequent to the first subsequent therapy or death †Calculated using the Kaplan–Meier technique §Calculated using stratified Cox proportional hazards model. A hazard ratio <1 favours capivasertib + fulvestrant.*
The log-rank test and Cox model were stratified by the presence of liver metastases (yes vs no), and prior use of CDK4/6 inhibitors (yes vs no) ***Source:*** *Clinical study report.*

Kaplan–Meier analysis of PFS2 data showed [redacted]

Figure 9. Kaplan–Meier plot of investigator-assessed PFS2 for the AKT pathway altered post CDK4/6i population (DCO2)

Source: Clinical study report.[80]

6.1.4.5 Time to treatment discontinuation (DCO2)

At DCO2, the median TTD was [redacted] for capivasertib ([redacted]) (Table 20). The TTD KM curve for capivasertib in the capivasertib + fulvestrant arm is presented in Figure 10. For fulvestrant as part of the capivasertib + fulvestrant combination, median TTD was [redacted] For fulvestrant in the fulvestrant + placebo arm, median TTD was [redacted] (Table 21). The TTD KM curves for fulvestrant in the capivasertib + fulvestrant arm and fulvestrant in the placebo + fulvestrant are presented in Figure 11. Relevant diagnostic plots are presented in the appendix (Appendix D.3).

Table 20. Time to treatment discontinuation estimates from the CAPItello-291 trial DCO2 (capivasertib) (AKT pathway altered post CDK4/6i)

Arm	N	Events	Maturity	Median, months (95% CI)
Capivasertib + Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]

Figure 10. CAPItello-291 DCO2 TTD KM curves for capivasertib and placebo (AKT pathway altered post CDK4/6i)

Table 21. Time to treatment discontinuation DCO2 estimates from the CAPItello-291 trial (fulvestrant in the capivasertib + fulvestrant arm and fulvestrant in the placebo + fulvestrant) (AKT pathway altered post CDK4/6i)

Arm	N	Events	Maturity	Median, months (95% CI)
Placebo + Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]
Fulvestrant (Capivasertib + Fulvestrant arm)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: CI, confidence interval

Figure 11. CAPItello-291 DCO2 TTD KM curves for fulvestrant in the capivasertib + fulvestrant arm and fulvestrant in the placebo + fulvestrant arm (AKT pathway altered post CDK4/6i)

6.1.5 Efficacy – results per [study name 2]

Not applicable

7. Comparative analyses of efficacy

As a head-to-head study (CAPItello-291) directly comparing the intervention and comparator was used to inform the health economic assessment, the following section describing comparative analysis is not of relevance.

7.1.1 Differences in definitions of outcomes between studies

Not applicable.

7.1.2 Method of synthesis

Not applicable.

7.1.3 Results from the comparative analysis

Not applicable.

Table 22. Results from the comparative analysis of [intervention] vs. [comparator] for [patient population]

Outcome measure	[Intervention] (N=x)	[Comparator] (N=x)	Result
[Outcome measure 1]	N/A	N/A	N/A
[Outcome measure 2]	N/A	N/A	N/A

7.1.4 Efficacy – results per [outcome measure]

Not applicable.

8. Modelling of efficacy in the health economic analysis

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

The efficacy inputs used for the health economic assessment of capivasertib were based on the CAPItello-291 trial and included PFS, TTD and OS. The AKT pathway altered post CDK4/6i patient group was used for the survival analysis. The analysis was based on DCO1 for PFS and DCO2 (interim analysis) for OS and TTD. PFS was not updated at DCO2 as the primary and final PFS analysis was based on DCO1. The median follow-up time for the AKT pathway altered post CDK4/6i subgroup by endpoint and by arm (capivasertib +fulvestrant and fulvestrant alone, respectively) was:

8.1.1 Extrapolation of efficacy data

8.1.1.1 Extrapolation of progression-free survival

The summary of assumptions associated with extrapolation of PFS is presented in Table 23.

Table 23. Summary of assumptions associated with extrapolation of PFS

Method/approach	Description/assumption
Data input	PFS – AKT pathway altered post CDK4/6i population of the CAPItello-291 trial (DCO1)

Method/approach	Description/assumption
Model	Eight standard parametric models were fitted to the individual patient data from CAPItello-291: Exponential, Weibull, Gompertz, Lognormal, Loglogistic, Generalised gamma, Gamma.
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	Capivasertib: Log-normal Fulvestrant: Log-logistic
Function with best BIC fit	Capivasertib: Log-normal Fulvestrant: Log-logistic
Function with best visual fit	Capivasertib: Log-normal, log-logistic Fulvestrant: Log-normal, log-logistic
Function with best fit according to evaluation of smoothed hazard assumptions	Capivasertib: Log-normal Fulvestrant: Log-normal
Validation of selected extrapolated curves (external evidence)	PFS had a high degree of data maturity (DCO1 was the final analysis of PFS). The reported median and restricted mean survival time (RMST) PFS for placebo + fulvestrant are [redacted], respectively. The extrapolated mean PFS based on the log normal distribution [redacted]) is well aligned with the reported RMST. The extrapolated median PFS [redacted]) is close to the reported median PFS, [redacted] With approximately [redacted] of patients still progression free for the capivasertib + fulvestrant arm at the first data cut, the mean PFS was expected to be longer compared to reported RMST PFS [redacted]) when extrapolated. The log normal generates the most plausible mean PFS estimate of [redacted]. The reported median PFS [redacted] is well aligned with the extrapolated median PFS ([redacted]).
Function with the best fit according to external evidence	Not assessed due to a high degree of data maturity for PFS.
Selected parametric function in base case analysis	Capivasertib: Log-normal Fulvestrant: Log-normal

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	No
Assumptions of cure point	No

The fit of the models to the observed KM data is shown in Figure 12 and Figure 13 (see Appendix D for figures with shorter follow up).

Figure 12. Fit of the parametric survival models to the capivasertib + fulvestrant DCO1 KM data for PFS in the AKT pathway altered post CDK4/6i population in CAPItello-291

Figure 13. Fit of the parametric survival models to the placebo + fulvestrant DCO1 KM data for PFS in the AKT pathway altered post CDK4/6i population in CAPItello-291

8.1.1.2 Extrapolation of overall survival

The summary of assumptions associated with extrapolation of OS is presented in Table 24.

Table 24. Summary of assumptions associated with extrapolation of OS

Method/approach	Description/assumption
Data input	OS - AKT pathway altered post CDK4/6i population of the CAPItello-291 trial (DCO2)
Model	Eight standard parametric models were fitted to the individual subject data from CAPItello-291: Exponential, Weibull, Gompertz, Lognormal, Loglogistic, Generalised gamma, Gamma.
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	Capivasertib: Gamma Fulvestrant: Exponential

Method/approach	Description/assumption
Function with best BIC fit	Capivasertib: Gamma Fulvestrant: Exponential
Function with best visual fit	Capivasertib: Gamma Fulvestrant: Gamma
Function with best fit according to evaluation of smoothed hazard assumptions	Capivasertib: Gamma Fulvestrant: Gamma The gamma distribution seems to be the best fit, capturing the shape of the hazard for both treatments until month [redacted].
Validation of selected extrapolated curves (external evidence)	RWE, Clinical expert opinions on clinical plausibility (disease course of mBC and treatment outcomes)
Function with the best fit according to external evidence	Capivasertib: Gamma Fulvestrant: Gamma
Selected parametric function in base case analysis	Capivasertib: Gamma Fulvestrant: Gamma There is no clinical rationale to assume differences in the shape of the hazard of death and consequently parametric function between capivasertib + fulvestrant and fulvestrant alone. Hence, the same distribution was selected for both treatments.
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	The fulvestrant hazard of death was used as a "hazard adjustment" for capivasertib to support clinical plausibility. See section 8.4.
Assumptions of cure point	No

The fit of the models to the observed KM data is shown in Figure 14 and Figure 15 (see Appendix D for figures with shorter follow up).

Figure 14. Fit of the parametric survival models to the capivasertib + fulvestrant DCO2 KM data for OS in the AKT pathway altered post CDK4/6i population in CAPItello-291

Figure 15. Fit of the parametric survival models to the placebo + fulvestrant DCO2 KM data for OS in the AKT pathway altered post CDK4/6i population in CAPItello-291

8.1.1.3 Extrapolation of time to next treatment

The summary of assumptions associated with extrapolation of TTD is presented in Table 25. TTD was extrapolated and included in the analysis for costing purposes only and does not impact the efficacy.

Table 25. Summary of assumptions associated with extrapolation of TTD

Method/approach	Description/assumption
Data input	TTD - AKT pathway altered post CDK4/6i population of the CAPItello-291 trial (DCO2)
Model	Eight standard parametric models were fitted to the individual subject data from CAPItello-291: Exponential, Weibull, Gompertz, Lognormal, Loglogistic, Generalised gamma, Gamma.
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	Capivasertib: Log-logistic Fulvestrant (capivasertib combination): Log-logistic Fulvestrant (monotherapy): Log-logistic
Function with best BIC fit	Capivasertib: Log-logistic Fulvestrant (capivasertib combination): Log-logistic Fulvestrant (monotherapy): Log-logistic
Function with best visual fit	Capivasertib: Log-logistic Fulvestrant (capivasertib combination): Log-logistic Fulvestrant (monotherapy): Log-logistic
Function with best fit according to evaluation of smoothed hazard assumptions	Capivasertib: Log-logistic Fulvestrant (capivasertib combination): Log-logistic Fulvestrant (monotherapy): Log-logistic
Validation of selected extrapolated curves (external evidence)	Not done due to a high degree of data maturity for TTD.
Function with the best fit according to external evidence	Not assessed due to a high degree of data maturity for TTD.
Selected parametric function in base case analysis	Capivasertib: Log-logistic Fulvestrant (capivasertib combination): Log-logistic Fulvestrant (monotherapy): Log-logistic

Method/approach	Description/assumption
Adjustment of background mortality with data from Statistics Denmark	No. TTD is limited by PFS.
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

The fit of the models to the observed KM data is shown in Figure 16 to Figure 18 (see Appendix D for figures with shorter follow up) .

Figure 16. KM curves and parametric models – Capivasertib – DCO2 TTD AKT pathway altered post CDK4/6i population

Figure 17. KM curves and parametric models – fulvestrant in the capivasertib + fulvestrant arm – DCO2 TTD AKT pathway altered post CDK4/6i population

Figure 18. KM curves and parametric models – fulvestrant in the placebo + fulvestrant arm – DCO2 TTD AKT pathway altered post CDK4/6i population

8.1.2 Calculation of transition probabilities

Not applicable due to a partitioned survival model structure.

Table 26. Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
N/A	N/A	N/A	N/A

8.2 Presentation of efficacy data from [additional documentation]

Not applicable.

8.3 Modelling effects of subsequent treatments

No adjustment on survival was implemented, [redacted] any survival benefit attributable to subsequent treatment is implicitly captured in the OS data. Further details on the proportion of patients, treatment duration and costs for subsequent treatment are presented in section 11.6.

8.4 Other assumptions regarding efficacy in the model

At DCO2 [redacted] of capivasertib patients and [redacted] of fulvestrant patients had progressed on subsequent treatment (Table 27 and Table 28 for the distribution of subsequent treatments).

Generally, there is strong empirical evidence in BC and other solid tumours demonstrating the surrogacy of PFS2 with OS [81-83], with the more frequent recurrences experienced by a patient, the higher their risk of death according to Lafourcade et al. (2018) [84]. The link between the progression frequency and OS was also discussed with a clinical expert: Slowing down the disease may translate into an overall prolonged OS [5]. Patients are likely to benefit from capivasertib not only during treatment but also experience slower disease progression and an extended time to the next treatment as evidenced by improved PFS and PFS2 in the CAPItello-291 trial.

After experiencing multiple disease progressions, it can be argued that patients who advance to an additional subsequent treatment (i.e., 4th+ line) have likely demonstrated a level of resilience that may be attributed to factors beyond just their treatment. If a patient has already survived through a more advanced treatment line (for example, the 4th + line), the patient has successfully managed previous challenges or complications. Conversely, patients who are weaker or have more severe disease may not live long enough to reach the 4th+ line of treatment.

Assuming consistent subsequent treatments, the impact of factors such as tumour biology, on the risk of death and prognosis increases. As a result, the risk of death is likely to become more similar among patients who have progressed through several lines of treatment, regardless of their prior treatment history.

Altogether, [redacted]. Only beyond 4th line, long-term survivors likely have similar hazards of death due to other factors than 2L treatment.

Table 27. DCO2 PFS2 events – AKT pathway altered post CDK4/6i

Arm	N	Events	Maturity	Median, months (95% CI)
Placebo + Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]
Capivasertib + Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: CI, confidence interval

Figure 19. CAPItello-291 DCO2 PFS2 KM curves for capivasertib + fulvestrant and fulvestrant + placebo (AKT pathway altered post CDK4/6i)

[redacted]

Table 28. Proportion of progressed disease patients receiving type of subsequent anti-cancer therapy in CAPItello-291 trial (AKT pathway altered post CDK4/6i population, DCO2)

Type of therapy	Capivasertib+fulvestrant arm (n=114)	Placebo+fulvestrant arm (n=94)
Any subsequent therapy, n (%)	[redacted]	[redacted]
Hormonal therapy, n (%)	[redacted]	[redacted]
Cytotoxic chemotherapy, n (%)	[redacted]	[redacted]
Antibody-drug conjugates, n (%)	[redacted]	[redacted]
Targeted therapy, n (%)	[redacted]	[redacted]
Antiangiogenetic therapy, n (%)	[redacted]	[redacted]
PARP inhibitor, n (%)	[redacted]	[redacted]
Biologic therapy, n (%)	[redacted]	[redacted]
Immunotherapy, n (%)	[redacted]	[redacted]

As mentioned above, capivasertib as a targeted add-on treatment to fulvestrant is not expected to result in a worse prognosis post treatment compared to fulvestrant mono-therapy, which is also supported by the statistically significant benefit observed in terms of PFS2 (section 6.1.4.4). It is anticipated that after undergoing multiple lines of treatment, patients in both arms will exhibit similar hazards of death. [redacted]

Figure 20. Hazard of death assumption (AKT pathway altered post CDK4/6i)

The respective landmark survival resulting from the gamma distribution [redacted] (i.e., base case approach) are presented in Table 29. [redacted] This pattern is reasonable considering the overall prognosis and course of the disease of mBC as described above.

Table 29. Landmark overall survival – base case (gamma distribution for both arms and merging hazards)

Treatment	1 years	2 years	3 years	5 years	10 years	20 years
Capivasertib + fulvestrant	[redacted]					
Fulvestrant	[redacted]					

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

The modelled and observed outcomes for PFS, OS and TTD are presented in Table 30 to Table 33.

Table 30. Estimates in the model – PFS

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
Capivasertib + fulvestrant	[redacted]	[redacted]	[redacted]
Fulvestrant alone	[redacted]	[redacted]	[redacted]

Table 31. Estimates in the model - OS

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
Capivasertib + fulvestrant	[redacted]	[redacted]	[redacted]
Fulvestrant alone	[redacted]	[redacted]	[redacted]

Table 32. Estimates in the model – TTD

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
Capivasertib	[redacted]	[redacted]	[redacted]
Fulvestrant (capivasertib combination)	[redacted]	[redacted]	[redacted]
Fulvestrant (monotherapy)	[redacted]	[redacted]	[redacted]

Table 33. Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

Treatment	Treatment length [months]	Progresssion free ‡ [months]	Post-progression ‡ § [months]
Capivasertib + fulvestrant	Capivasertib: [redacted] Fulvestrant: [redacted]	[redacted]	[redacted]
Fulvestrant alone	[redacted]	[redacted]	[redacted]

* TTD is controlled by PFS (the TTD value per cycle cannot be higher than the PFS value of the same cycle)
‡ PFS and OS are controlled for general population background mortality (the risk of a PFS or OS event per cycle cannot exceed the risk of background mortality of the same cycle).

§ OS is controlled by PFS since the PFS outcome is more mature.

9. Safety

9.1 Safety data from the clinical documentation

Overall, the AEs reported in this study were consistent with the known safety profiles of capivasertib and fulvestrant or, were due to underlying disease. Assuming that alterations in the AKT pathway and exposure to CDK4/6i do not affect the safety profile of capivasertib, the safety analysis from the overall population serves as the foundation for this assessment, as it represents the most comprehensive dataset (safety analysis set (SAS) for the complete trial population). An overview of serious adverse events for the SAS is presented in Table 34. Refer to Appendix L for a summary of all reported AEs (DCO2) in the SAS population (Table 106).

Table 34. Overview of safety events in the SAS at DCO2

	Capivasertib + fulvestrant (N=355) (CAPItello-291, SAS)‡	Placebo + fulvestrant (N=350) (CAPItello-291, SAS)±	Difference, % (95 % CI)
Number of adverse events, n	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥1 adverse events, n (%)	[redacted]	[redacted]	[redacted]
Number of serious adverse events*, n	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥ 1 serious adverse events**, n (%)	[redacted]	[redacted]	[redacted]
Number of CTCAE grade ≥ 3 events, n	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	[redacted]	[redacted]	[redacted]
Number of adverse reactions, n	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥ 1 adverse reactions, n (%)†	[redacted]	[redacted]	[redacted]

	Capivasertib + fulvestrant (N=355) (CAPItello-291, SAS)‡	Placebo + fulvestrant (N=350) (CAPItello-291, SAS)±	Difference, % (95 % CI)
Number and proportion of patients who had a dose reduction, n (%)	[redacted]	[redacted]	[redacted]
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	[redacted]	[redacted]	[redacted]
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	[redacted]	[redacted]	[redacted]

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

§ CTCAE v. 5.0 (23 September 2018) is used.

** SAEs reported in two or more patients in either treatment arm

†Patients with AE of CTCAE grade 3 or higher, possibly related to capivasertib/placebo only

‡Based on the median exposure time of [redacted] months for capivasertib and [redacted] months for fuvlestrant (DCO2)

± Based on the median exposure time o[redacted] months for placebo and 3.68 months for fuvlestrant (DCO2)

[redacted]

Table 35. Serious adverse events (DCO2 – Reported in ≥ 2 Patients in Either Treatment Arm (SAS))

Adverse events	Capivasertib + fulvestrant (N=355) (CAPItello-291, SAS)		Placebo + fulvestrant (N=350) (CAPItello-291, SAS)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with any SAE	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Rash maculopapular†	[redacted]	[redacted]	[redacted]	[redacted]

Adverse events	Capivasertib + fulvestrant (N=355) (CAPItello-291, SAS)	Placebo + fulvestrant (N=350) (CAPItello-291, SAS)
Vomiting	[redacted]	
Acute kidney injury		
Hyperglycaemia		
Asthenia		
Pneumonia aspiration		
Sepsis		
COVID-19		
Pyrexia		
Pyelonephritis	[redacted]	
Diabetic ketoacidosis		
Stomatitis		
Pneumonia		
Hypercalcaemia		
Nausea		
Anaemia		
Platelet count decreased		

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

In the capivasertib + fulvestrant arm, the incidence of AEs with an outcome of death during the study treatment period (including 30-day follow-up) was low [redacted] were considered related to capivasertib (refer to Table 36). [redacted]

Table 36. Summary of Deaths (FAS) Number (%) of patients

Adverse events	Capivasertib + fulvestrant (N=355) (CAPItello-291, SAS)	Placebo + fulvestrant (N=350) (CAPItello-291, SAS)
Total number of deaths	[redacted]	
Death related to disease under investigation only [a]		
AE with outcome of death only [b]		
AE with outcome of death and death related to disease under investigation [b]		
AE with outcome of death and AE onset date falling after 30 (+ 7) days following last dose of study treatment		
Other deaths [c]		

a Death related to disease under investigation is determined by the investigator.

b AEs with an onset date on/after date of first dose; AEs with onset date prior to dosing which worsen after dosing; AEs occurring up to 30 days (+ 7 days) following date of last dose are reported.

c Patients who died and are not captured in the earlier categories.

Source: Table 20, CSR ver2

The economic analysis includes AEs that were classified as CTCAE Grade 3 or above and with frequency of > 2%, to ensure that key events that would have a meaningful impact on cost and QALYs were captured (Table 37). The costs and health effects of Grade 1 and 2 events are assumed to be negligible and therefore omitted from the analysis.

Table 37. Adverse events used in the health economic model

Adverse events	Capivasertib + fulvestrant (N=355) (CAPItello-291, SAS)	Placebo + fulvestrant (N=350) (CAPItello-291, SAS)		
	Frequency used in economic model		Source	Justification

Adverse events	Capivasertib + fulvestrant (N=355) (CAPItello-291, SAS)	Placebo + fulvestrant (N=350) (CAPItello-291, SAS)		
Adverse event, n (%)	[redacted]		CAPItello-291 DCO2	AEs of CTCAE grade 3 or higher, most common (frequency of > 2%)
Diarrhoea				
Rash maculo-papular				
Rash				
Hyperglycaemia				
Hypokalaemia				
Anaemia				
Aspartate aminotransferase increased				
Alanine aminotransferase increased				
Stomatitis				

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

Not applicable.

Table 38. Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

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

In CAPItello-291, health related quality of life (HRQoL) was assessed using the EORTC instrument and by the EQ-5D-5L questionnaire.

The following sections present the EQ-5D-5L only as this instrument was used for estimating HRQoL inputs for this assessment.

Table 39. Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	CAPItello-291	Describe purpose of HRQoL instrument (clinical effectiveness, utilities, disutilities etc.)
EQ-VAS	CAPItello-291	

10.1 Presentation of the health-related quality of life CAPItello-291

10.1.1 Study design and measuring instrument

The EuroQoL 5 Dimensions 5 levels (EQ-5D-5L) and EuroQoL visual analogue scale (EQ-VAS) measurements were collected in CAPItello-291.

10.1.2 Data collection

EQ-5D data was collected on day 1, during the first week of every treatment cycle (4 weeks). The pattern of missing data and completion for the first 12 cycles are presented in Table 40. See appendix F, Table 78 for the full table.

Table 40. Pattern of missing data and completion

Time point	Treatment group	Expected[a]	Received[b]	Evaluable[c]	Compliance rate (%)[d]	Evaluability rate (%)[e]
Overall	Capi + Fulv	[redacted]				
	Pbo + Fulv					
Baseline	Capi + Fulv					
	Pbo + Fulv					
Cycle 2 Week 1 Day 1	Capi + Fulv					
	Pbo + Fulv					

Cycle 3 Week 1 Day 1	Capi + Fulv	[redacted]
	Pbo + Fulv	
Cycle 4 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	
Cycle 5 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	
Cycle 6 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	
Cycle 7 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	
Cycle 8 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	
Cycle 9 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	
Cycle 10 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	
Cycle 11 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	
Cycle 12 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	

Abbreviations: Capi, capivasertiv; Fulv, fulvestrant; Pbo, Placebo. In the overall row, patients are counted as Received/Evaluable if they have a Received/Evaluable baseline and at least one Received/Evaluable post-baseline form. Time points are reported by visit for each treatment group, provided at least one group has ≥ 20 patients with data at a given visit

[a]Number of patients who has not withdrawn from the study at given time point

[b]The number of patients who completed at a given time point

[c]Number of patients with forms where at least one subscale can be determined

[d]100%*Evaluable/Expected

[e]100%*Evaluable/Received

10.1.3 HRQoL results

The mean change from baseline and the summary statistics are presented in Figure 21 and Table 41, respectively.

Figure 21. Mean change from baseline through the different data collection time points

Table 41. HRQoL EQ-5D-5L summary statistics

Scale / Timepoint	Capivasertib + fulvestrant		Placebo + fulvestrant		Capivasertib + fulvestrant vs. placebo + fulvestrant
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]				
Cycle 2 Week 1 Day 1					
Cycle 3 Week 1 Day 1					
Cycle 4 Week 1 Day 1					
Cycle 5 Week 1 Day 1					
Cycle 6 Week 1 Day 1					
Cycle 7 Week 1 Day 1					
Cycle 8 Week 1 Day 1					
Cycle 9 Week 1 Day 1					
Cycle 10 Week 1 Day 1					
Cycle 11 Week 1 Day 1					
Cycle 12 Week 1 Day 1					
Cycle 13 Week 1 Day 1					
Cycle 14 Week 1 Day 1					
Cycle 15 Week 1 Day 1					

Cycle 16 Week 1 Day 1	[redacted]
Cycle 17 Week 1 Day 1	
Cycle 18 Week 1 Day 1	
Cycle 19 Week 1 Day 1	
Cycle 20 Week 1 Day 1	
Cycle 21 Week 1 Day 1	
Cycle 22 Week 1 Day 1	
Cycle 23 Week 1 Day 1	
Cycle 24 Week 1 Day 1	
Cycle 25 Week 1 Day 1	
Cycle 26 Week 1 Day 1	
Cycle 27 Week 1 Day 1	
Cycle 28 Week 1 Day 1	
Cycle 29 Week 1 Day 1	
Cycle 30 Week 1 Day 1	
Cycle 31 Week 1 Day 1	
Cycle 32 Week 1 Day 1	
Cycle 33 Week 1 Day 1	
Cycle 34 Week 1 Day 1	
Cycle 35 Week 1 Day 1	

Cycle 36 Week 1 Day 1	[redacted]
Cycle 37 Week 1 Day 1	
Cycle 38 Week 1 Day 1	
Cycle 39 Week 1 Day 1	

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

As health state utility (HSU) data from the CAPItello-291 was available, no literature-based values were used for the base case analysis.

10.2.1 HSUV calculation

The health state utilities values (HSUV) were summarized using descriptive statistics and mixed effects repeated measures regression (MMRM) analysis. To maximise sample size, the analysis was based on data from the biomarker unselected (ITT) population of DCO2 of CAPItello-291 under the assumption that biomarker status is unlikely to impact on HSU. Please note that data limited to the AKT pathway altered subgroup is not available, thus the ITT data was considered an appropriate proxy and is applied to estimate the HSUVs.

For more information see Appendix F.

Age adjustment was applied according to the DMC methods guide [85].

10.2.1.1 Mapping

The values from the EQ-5D-5L profiles in CAPItello-291 were mapped using Danish preference weights [86]. Please refer to Appendix F for further information on the analysis.

10.2.2 Disutility calculation

A one-off QALY adjustment for AEs was modelled based on each AE's respective disutility (loss of utility) multiplied by its duration. The impact of AEs experienced by patients receiving subsequent treatment is not considered in the analysis. These AEs would impact both arms of the model, and therefore have a minimal influence on incremental results.

The economic analysis only includes AEs that were:

- Grade ≥3: AEs were included if they were classified as CTCAE Grade 3 or above. The disutilities related to Grade 1 and 2 events are assumed to be negligible and therefore omitted from the analysis.
- ≥2% of patients: to ensure that key events were captured while ensuring the list of included events was manageable.

A summary of the AEs included in the economic analysis, their associated disutilities, durations and respective sources is presented in Table 42. To represent the most complete dataset and under the assumption that biomarker status is unlikely to impact on AE, the incidence of AEs in the ITT SAS applies as a proxy for the AKT pathway altered post CDK4/6i population in CAPItello-291.

10.2.3 HSUV results

The HSUVs are presented in Table 42.

Table 42. Overview of health state utility values and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments	Reference
HSUVs					
Progression-free	[redacted]	EQ-5D-5L	DK	Mean estimate from both trial arms (DCO2)	
Progressed disease		EQ-5D-5L	DK	Estimate is based on mean of both trial arms (DCO2).	
Disutilities					
Diarrhoea	0.0468	EQ-5D-3L*	UK†	NR	Nafees et al. [64]
Rash	0.03248	EQ-5D-3L*	UK†	NR	Nafees et al. [64]
Hyperglycaemia	0.09	EQ-5D-3L	UK†	NR	Smith-Palmer et al. [65]
Hypokalaemia	0.1	EQ-5D-3L	UK†	Reduction in functional capacity by NYHA class indicating how much cardiac disease limits physical activity	Bounthavong et al. [66]
Anaemia	0.119	EQ-5D-3L*	UK	0.795 (stable with no AE) – 0.676 (stable with aneamia grade III) = 0.119 (anaemia)	As per TA563, Swinburn et al. [67, 68]
AST increased	0			Assumed no effect on QoL as they are only laboratory identified AEs	
ALT increased	0				
Stomatitis	0.151	EQ-5D*	UK		Lloyd et al. [69]

Abbreviations: AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; NYHA, New York Heart Association * The study utilized the EQ-5D instrument. However, the document does not specify whether the 3-level (3L) or 5-level (5L) version of the EQ-5D was used. Given the publication date of the study (<=2010), it is assumed that the EQ-5D-3L version was used. †The document does not specify the exact tariffs used. It is likely that the UK tariffs was used.

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

Not applicable.

10.3.1 Study design

Not applicable.

10.3.2 Data collection

Not applicable.

10.3.3 HRQoL Results

Not applicable.

10.3.4 HSUV and disutility results

Not applicable.

Table 43. Overview of health state utility values [and disutilities] – N/A

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs _ NA				
HSUV A - NA				
HSUV B - NA				
...				
[Disutilities] - NA				
...				

Table 44. Overview of literature-based health state utility values – N/A

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUV A – NA				
Study 1 – NA				
Study 2 – NA				
Study 3 - NA				

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUV B – NA				
...				
[Disutility A] - NA				
...				

11. Resource use and associated costs

The health economic analysis includes medicine acquisition and administration costs, testing costs, costs associated with disease management and terminal care, the management of adverse events, as well as non-medical costs. All costs are reported in DKK at the 2025 cost level. Resource use was validated by a Danish clinical expert [5].

11.1 Medicines - intervention and comparator

The assumptions for the drug acquisition costs as well as the cost inputs for capivasertib and fulvestrant are presented in Table 45 and Table 46, respectively.

Table 45. Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Truqap	400 mg (two 200 mg tablets)	[redacted]	Twice daily (for 4 days followed by 3 days off-treatment).	No
Fulvestrant	500 mg	[redacted]	Day 1 of Weeks 1 and 3 of cycle 1, and then on Day 1, Week 1 of each cycle thereafter	No

Table 46. Drug acquisition costs used in the model

Medicine	Strength	Package size	Pharmacy purchase price [DKK]
Intervention: Truqap + fulvestrant			

Medicine	Strength	Package size	Pharmacy purchase price [DKK]
Truqap	200 mg	4 x 16 blisters	41,034.97
	160 mg	4 x 16 blisters	41,034.97
Fulvestrant	500 mg	2 x 250 mg	462.00
Comparator: Fulvestrant monotherapy			
Fulvestrant	500 mg	2 x 250 mg	462.00

Dose reduction

Dose reductions may be appropriate during the treatment with capivasertib while re-escalation is not anticipated. Second dose reductions were accounted for in the health economic analysis. Assuming no difference in price between 200mg and 160mg packages of capivasertib, only the second reduction has an impact on the acquisition costs (i.e., same price for 160mg and 200mg strength packages of 64 tablets).

Data on dose reductions was not available for the AKT pathway altered post CDK4/6i patient cohort. [redacted]. Dose reductions were not assumed to have any impact on the efficacy outcomes in the analysis as these are reflected in the CAPItello-291 trial data.

Table 47. Dose reductions for capivasertib

Number of reductions	Capivasertib + fulvestrant in the CAPItello-291 trial (DCO2, SAS) (n=355)	Health economic model input
One reduction	[redacted]	
Two reductions		
More than two reductions		

Abbreviations: DCO, Data cut off; SAS, safety analysis set * Per protocol, a maximum of 2 dose reductions were allowed for toxicity management. No dose re-escalation was allowed. Data inconsistencies were identified for [redacted] patients with more than 2 dose reduction actions recorded within the electronic medical record; however, all [redacted] patients appear to be reporting missed or forgotten doses (interruptions) incorrectly as dose reductions. None of the [redacted] patients reduced to < 200 mg BD 4 days on/3 days off for routine dosing. No dose re-escalation occurred in these patients.

Wastage

No wastage was included in the analysis. Capivasertib is an oral treatment, and the cost was calculated on a monthly basis, regardless of whether the patient received treatment for the entire month or not. For fulvestrant no wastage was assumed as the vial size is in line with recommended dose and no dose adjustments are assumed. Hence, no waste may occur when being administered. For subsequent treatments (IV treatments specifically) no wastage was included as it affects both treatment arms similarly and the impact of potential waste on the ICER is expected to be minor.

Treatment duration

TTD data from the CAPItello-291 AKT pathway altered post CDK4/6i population was extrapolated using standard parametric survival models to estimate the drug acquisition costs for capivasertib + fulvestrant independent of the treatment outcomes (see 8.1.1.3). For costing purposes, TTD for capivasertib and fulvestrant was estimated separately despite being administered as combination therapy.

Based on the assumption that patients would terminate treatment upon disease progression, the TTD curve was limited by the PFS curve, i.e. the TTD curves could not exceed PFS. The estimated treatment duration, i.e., TTD is presented in Table 32.

11.2 Medicine– co-administration

Not applicable

11.3 Administration costs

Administration costs were applied for IV therapies (subsequent treatments). The cost of intramuscular injection (fulvestrant) was assumed to be covered by the monthly community nurse visits (see Table 49). No costs were assumed for oral administration as it does not require clinic visits. An overview of the administration costs is presented below (Table 48.

Table 48. Administration costs used in the model

Administration type	Unit cost [DKK]	DRG code	Reference
Intravenous administration	1,578	09MA98, MDC09 1-dagsgruppe, pat. mindst 7 år - Diagnosis code: DC509, Brystkræft UNS - Treatment code: BWAA30, Medicingivning ved intramuskulær injektion	2025 DRG [75]

*IV administration was included for subsequent treatments, i.e., chemotherapy (see section 11.6)

11.4 Disease management costs

11.4.1 Disease management costs

The costs associated with the health care resource use and respective utilization frequencies are presented in Table 49. The disease management activities and respective frequencies were validated by a Danish clinical expert to reflect the Danish setting [5].

Table 49. Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Oncology consultant office	Every 12 weeks for ET based regimen (2L), every 11 weeks if on chemotherapy (3L+)	1,578	2025 DRG code: 09MA98, MDC09 1-dagsgruppe, pat. mindst 7 år; Diagnosis code: DC509, Brystkræft UNS	DRG 2025 [75]
Community nurse*	Every four weeks for ET, every 12 weeks if on chemotherapy	1,578	2025 DRG code: 09MA98, MDC09 1-dagsgruppe, pat. mindst 7 år; Diagnosis code: DC509, Brystkræft UNS	
Clinical nurse specialist	Every 12 weeks for ET based regimen (2L), every three weeks if on chemotherapy (3L+)	1,578	2025 DRG code: 09MA98, MDC09 1-dagsgruppe, pat. mindst 7 år; Diagnosis code: DC509, Brystkræft UNS	
Computed tomography (CT) scan - thoracic & abdomen	Every three to four months	2,585	2025 DRG code: 30PR06, CT-scanning, kompliceret - Diagnosis code: DC509, Brystkræft UNS - Procedure code: UXCD00, CT-skanning af abdomen	
Blood test (Full blood count)	Every three months for ET based regimen (2L), every three weeks if on	1,578	2025 DRG code: 09MA98, MDC09 1-dagsgruppe, pat. mindst 7 år; Diagnosis code:	

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
	chemotherapy (3L+)		DC509, Brystkræft UNS	

*Assumed to include the administration of fulvestrant (intramuscular injection)

11.4.2 Treatment specific monitoring costs

In line with the marketing authorization for capivasertib [87], fasting glucose levels should be monitored at weeks 1, 2, 4, 6 and 8 after treatment start and monthly thereafter, additionally, it is recommended to test fasting blood glucose levels pre-dose at day 3 or 4 of the dosing week. HbA1c should be monitored every 3 months after initiating treatment with capivasertib (see Table 5). Patient costs for treatment-specific monitoring were not included, as these are likely covered under standard care, i.e., patients would not require additional visits specifically for monitoring while receiving capivasertib.

This treatment-specific monitoring was accounted for in the health economic assessment (see Table 50).

Table 50. Treatment-specific monitoring inputs for capivasertib

	Frequency per month	Cost (DKK)	Cost per month (DKK)	Reference
Fasting glucose	1		9	
Fasting glucose at treatment initiation (one off cost for week 2 and 6 of treatment)	2*	9	18 (one-off)	P-Glukose [88]
HbA1c	0.33	20	7	Hb(B)-Hæmoglobin A1c [88]

*To account for increased testing at treatment initiation, two additional tests were included as a one-off cost (representing week 2 and 6 of treatment). Week 1, 4, and 8 are covered by the regular monthly tests.

11.5 Costs associated with management of adverse events

Costs linked to AEs were applied as a one-off event in the first model cycle with the incidence data and unit cost covering the entire time on treatment. Patients were assumed to only experience the consequences of AEs once, regardless of the time on treatment. Only AEs of grade ≥3 occurring in at least 2% of the CAPItello-291 study population were included in the base case analysis. The respective frequencies for the AEs included in the base case are described in section 9.1.

The AE management costs were sourced from the Danish DRG list for 2025 (Table 51) [75]. The costs were applied additional to routine care assuming that patients require resources beyond the regular follow-up care.

Table 51. Cost associated with management of adverse events

	DRG code [75]	Unit cost (DKK)
Diarrhoea	06MA11, Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag. - Diagnosis code: DK529B, Ikke-infektiøs diarré UNS	4,977
Cost Rash maculo-papular	09MA98, MDC09 1-dagsgruppe, pat. mindst 7 år - Diagnosis code: DL270, Generaliseret dermatitis forårsaget af indtaget lægemiddel	1,578
Rash	09MA98, MDC09 1-dagsgruppe, pat. mindst 7 år - Diagnosis code: DR219, Hududslæt UNS	1,578
Hyperglycaemia	23MA03, Symptomer og fund, u. kompl. bidiag. - Diagnosis code: DR739, Hyperglykæmi UNS	5,271
Hypokalaemia	10MA98 MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis code: DE835C Hyperkaliæmi	1,992
Anaemia	16MA98 MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis code: HDD649 Anæmi UNS	2,208
Aspartate aminotransferase increased	07MA98 MDC07 1-dagsgruppe, pat. mindst 7 år, Diagnosis code: HDR945 Abnorm leverfunktionsundersøgelse	2,072
Alanine aminotransferase increased	07MA98 MDC07 1-dagsgruppe, pat. mindst 7 år, Diagnosis code: HDR945 Abnorm leverfunktionsundersøgelse	2,072
Stomatitis	03MA98 MDC03 1-dagsgruppe, pat. mindst 7 år, Diagnosis code: DK121B Stomatitis UNS	2,060

11.6 Subsequent treatment costs

In total, 80% of patients were expected to receive subsequent treatments following disease progression based on clinical expert opinion [5]. Subsequent treatment costs were included as a weighted average and applied as a one-off cost upon progression. Since mBC treatment pathways vary widely, a simple one-off cost was considered reasonable due to the complexity of modeling a specific treatment flow. As patients receiving either capivasertib + fulvestrant or fulvestrant monotherapy may be eligible for similar subsequent therapies, this cost modeling approach likely has a negligible impact on cost-effectiveness results.

The share of patients receiving each one of the subsequent treatments as well as average treatment duration and posology were estimated and validated by Danish clinical expert [5]. No waste was assumed (see section 11.1).

For the IV administered chemotherapy the cost of IV administration was added to the monthly cost of treatment for the number of monthly administrations (in line with the posology (see section 11.3). The IV administration cost of 1,578 DKK has been used, as listed in Table 46 [75]. For the one-off cost, no half-cycle correction was applied as this would not reflect the true number of disease progressions during the first month of treatment. This in turn would lead to an underestimation of subsequent treatment costs.

Drug acquisition costs for subsequent treatments are presented in Table 53. The dosing assumptions for subsequent treatments are presented in Table 52. The exclusion of subsequent treatment costs was explored in a scenario analysis.

Table 52. Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing	Treatment duration*
Capecitabine	1250 mg/m2 administered	100% (assumption)	twice daily for 14 days followed by a 7-day rest period	No	6.1 months
Eribulin	1.23 mg/m2	100% (assumption)	on days 1 and 8 of every 21-day cycle	No (assumption)	3.7 months
Paclitaxel	80 mg/m2	100% (assumption)	every 7 days	No (assumption)	10.3 months

* Representing 3rd + line based on assumption and discussed with clinical expert [5].

Table 53. Drug acquisition costs used in the model – subsequent treatments

Medicine	Strength	Package size	Pharmacy purchase price [DKK]
Capecitabine	500 mg	120	545
Eribulin	0.44 mg/ml	2 ml	2,080
Paclitaxel	6 mg/ml	50 ml	201.5

11.7 Patient costs

A limited societal perspective was considered for the health economic assessment including patient costs and transportation costs [62]. Routine care (clinic visits) were included in

line with the DMC's catalogue of unit costs [89]. See Table 54 and Table 55 for the patient costs and assumptions. A payer perspective excluding patient costs was explored in a scenario analysis.

Table 54. Patient costs used in the model

Activity	Assumption	Cost (DKK)	Source
Patient time	1 h	188	[89]
Transportation	Roundtrip	144	[89]

Table 55. Assumptions - patient costs related to disease management

Activity	Frequency per month* - PFS	Frequency per month* - PD	Duration (h)
	Patient cost – disease management		
Oncology consultant office	0.36	0.4	1
Clinical nurse specialist	0.36	1.45	1
Community nurse visit	1.09	0.36	1

Abbreviation: IM, intramuscular; PFS, Progression-free survival; PD, Progressed disease *Based on disease management assumptions presented in section 11.4.

Patient time and transportation costs has also been calculated for management of AEs. See Table 56 for the assumptions related to AE management. Patient costs related to adverse events (AEs) are based exclusively on AEs requiring hospitalization, with an assumed duration of hospitalization of 3 days per event (total of 72 patient hours). The remaining AEs are assumed to be managed within routine visits due to a lack of specific data. The proportion of AEs leading to hospitalization is informed by Rugo et al. (CAPItello-291) [90], which details the limited incidence of hospital admissions due to AE management in this setting. Patient-related costs are applied as a one-off cost in the model (first cycle only).

Table 56. Assumptions – AE leading to hospitalization, %

Activity	Capivasetib + fulvestrant (n=355)	Placebo + fulvestrant (n=350)
[redacted]		

Abbreviation: AE: adverse event

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

Testing cost

Incorporating testing for AKT pathway alterations into the current standard of care is anticipated to lead to a modest potential increase in costs. The expenses associated with testing for AKT pathway alterations were estimated based on the cost of PCR testing (1,200 DKK), as outlined in the price list published by Odense Universitetshospital [91]. It is estimated that, to identify one patient eligible for capivasertib, 2.45 patients would need to be tested (Table 57). A total testing cost of DKK 2,940 per eligible patient was included in the base case analysis. The exclusion of testing costs was explored in a scenario analysis.

Table 57. Testing costs used in the model

Parameter	Value	Reference
Proportion of PIK3CA/AKT1/PTEN - altered tumour tissue	40.8%	CAPItello-291 data: The overall proportion of patients with PIK3CA/AKT1/PTEN alterations detected in their tumour samples (i.e., the Altered Population) was 40.8% (289 of 708 patients)
Number of patients needed to test to identify one eligible patient	2.45	Assumption (1/0.408)
Cost of testing	DKK 1,200	Cytogenetiske analyser - PCR analyse [91]
Total testing cost per eligible patient	DKK 2,940	

Terminal care cost

A terminal care cost of DKK 135,121 was applied as a one-off cost upon death based on a publication by Round et al. [74]. The authors estimated the cost of caring for people with cancer at the end of life including health, social, informal, and charity care using UK-based studies. The mean cost of £12,663 was converted to DKK and inflated to the 2024 price level (full year) [92]. It was assumed that the cost is representative of the Danish setting.

12. Results

12.1 Base case overview

An overview of base case assumptions is presented in Table 58.

Table 58. Base case overview

Feature	Description
Comparator	Fulvestrant
Type of model	Partitioned survival model
Perspective	Limited societal perspective
Time horizon	20 years (lifetime)
Treatment line	2nd line in the metastatic setting, post CDK4/6i
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in study CAPItello-291 [63]. Danish population weights were used to estimate health-state utility values
Costs included	Medicine costs (incl. admin and subsequent treatments) Testing costs Disease management costs (incl. treatment specific monitoring) Costs of adverse event management Patient costs End of life/ palliative care costs
Dosage of medicine	In line with the label
Average time on treatment	Capivasertib: [redacted] months Fulvestrant (in combination with capivasertib) [redacted] months Fulvestrant monotherapy: [redacted] months
Parametric function for PFS	Capivasertib + fulvestrant: Log-normal Fulvestrant alone: Log-normal
Parametric function for OS	Capivasertib + fulvestrant: Gamma Fulvestrant alone: Gamma Hazard adjustment applied
Inclusion of waste	Not included
Average time in model health state	Capivasertib + fulvestrant:
Progression-free	[redacted] months
Progressed disease	[redacted] months (OS-PFS)

Feature	Description
	Fulvestrant alone:
Progression-free	[redacted] months
Progressed disease	[redacted] months (OS-PFS)

12.1.1 Base case results

Base case results are presented in Table 59. The total costs for capivasertib + fulvestrant amount to 805,655 DKK, resulting in a difference of 432,790 DKK compared to fulvestrant alone. In terms of progression-free life years, the combination therapy provides 0.76 years compared to 0.37 years with monotherapy, a difference of 0.39 years. Total life years for patients treated with capivasertib + fulvestrant are 2.73, versus 2.38 for those receiving only fulvestrant. The total difference in QALYs is 0.28. The incremental cost QALY gained stands at 1,540,711 DKK.

Table 59. Base case results, discounted estimates

	Capivasertib + fulvestrant	Fulvestrant mono-therapy	Difference
Medicine costs (DKK)	412,790	2,600	410,191
Administration (DKK)	0	0	0
Disease management costs (DKK)	192,007	175,473	16,535
Treatment specific monitoring costs (DKK)	164	0	164
Management of adverse events (DKK)	1,711	199	1,512
Subsequent treatment costs (DKK)	47,551	47,951	-400
Patient costs (DKK)	23,430	20,354	3,076
Palliative care costs (DKK)	125,062	126,288	-1,226
Testing costs (DKK)	2,940	0	2,940
Total costs (DKK)	**805,655**	**372,865**	**432,790**
Progression Free (LY)	**0.76**	**0.37**	**0.39**
Progressed Disease (LY)	**1.97**	**2.01**	**-0.04**
Total life years	**2.73**	**2.38**	**0.35**
Progression Free (QALY)	0.64	**0.31**	**0.33**
Progressed Disease (QALY)	1.55	1.58	-0.03
Adverse reactions (QALY)	-0.02	0.000	-0.02
Total QALYs	**2.18**	**1.90**	**0.28**
Incremental costs per life year gained (DKK)			**1,238,443**
Incremental cost per QALY gained (ICER) (DKK)			**1,540,711**

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

Scenario analyses

The results of other scenario analyses are presented below in Table 60. The scenario analysis reveals that the ICER varies across different assumptions, ranging from 1,448,641 DKK to 1,638,275 DKK. Most scenarios result in an ICER close to the base case of 1,540,711 DKK, suggesting robustness. Changing the survival distribution for PFS to a Generalized gamma distribution leads to the highest ICER, while using a Gompertz distribution for OS results in the lowest ICER among the tested scenarios.

Table 60. Scenario analysis

Base case input	Scenario analysis	ICER (DKK)	Change from base case ICER (DKK)
Base case		1,540,711	-
Age: 57.7 years, Time horizon: 20 years	Age: 69 years, Time horizon: 11 years	1,557,993	17,282
Limited societal perspective	Payer perspective	1,531,806	-8,904
Log normal for capivasertib + fulvestrant and fulvestrant monotherapy - PFS	Log-logistic	1,619,596	78,885
	Generalized gamma	1,638,275	97,564
Gamma distribution for capivasertib + fulvestrant and fulvestrant monotherapy – OS (incl. hazard adjustment)	Weibull	1,539,797	-913
	Gompertz	1,448,641	-92,070
Subsequent treatment costs included	No subsequent treatment costs	1,542,133	1,422
Testing costs included	No testing costs	1,530,245	-10,466

No wastage due to dose reduction	Wastage included*	1,562,331	21,620

Abbreviations: OS, overall survival; PFS, progression-free survival

[redacted] of the capivasertib treated patients experienced at least one dose reduction and therefore they were assumed to waste half package in the first model cycle as per DMC request

Deterministic sensitivity analysis

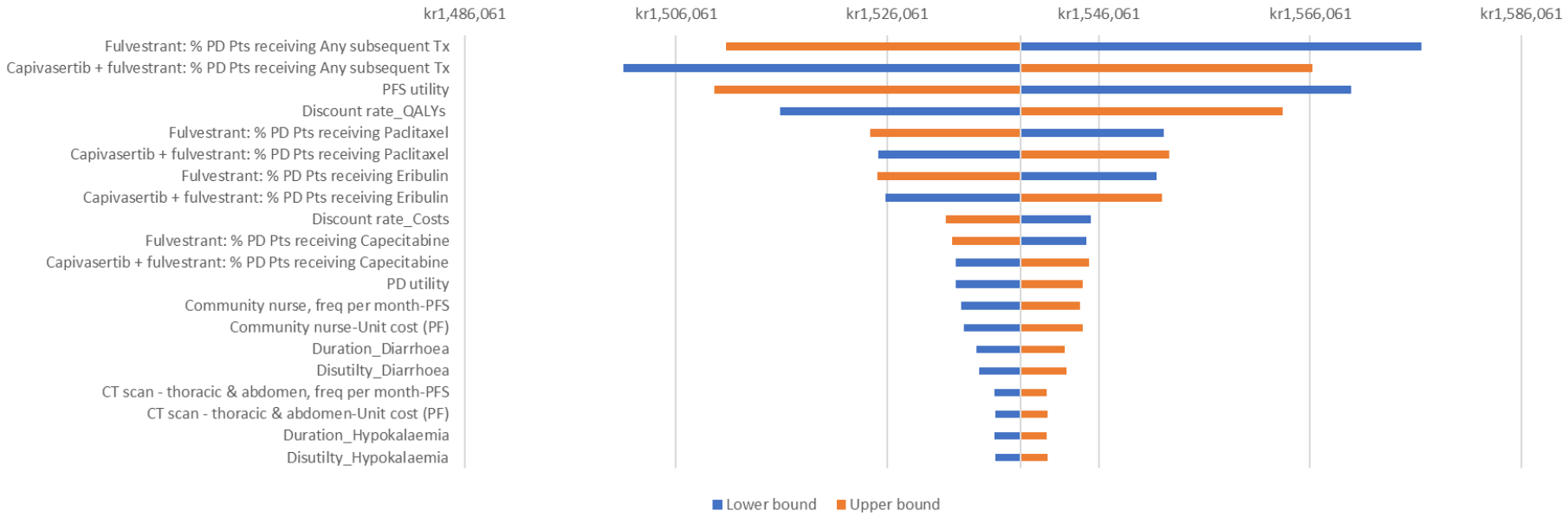
Results of the deterministic sensitivity analysis is presented in Figure 22 and Table 61. The top three parameters which had the greatest impact on the ICER were the proportion (%) of patients in the PD state receiving any subsequent treatment (for patients in both arms), and the HSUV in progression-free health state. The results appear overall robust.

Table 61. One-way sensitivity analyses results

	Input value			Results (kr/QALY gained)	
	Base case value	Lower bound	Upper bound	Lower bound	Upper bound
Parameter					
Fulvestrant: % PD Pts receiving Any subsequent Tx	0.800	0.62	0.93	1,576,575	1,510,789
Capivasertib + fulvestrant: % PD Pts receiving Any subsequent Tx	[redacted]			1,501,071	1,566,309
PFS utility				1,569,942	1,509,673
Discount rate_QALYs	0.035	0.03	0.04	1,515,943	1,563,480
Fulvestrant: % PD Pts receiving Paclitaxel	0.333	0.27	0.40	1,552,203	1,524,453
Capivasertib + fulvestrant: % PD Pts receiving Paclitaxel	0.333	0.27	0.40	1,525,240	1,552,759
Fulvestrant: % PD Pts receiving Eribulin	0.333	0.27	0.40	1,551,538	1,525,151
Capivasertib + fulvestrant: % PD Pts receiving Eribulin	0.333	0.27	0.40	1,525,900	1,552,067
Discount rate_Costs	0.035	0.03	0.04	1,545,308	1,531,598
Fulvestrant: % PD Pts receiving Capecitabine	0.333	0.27	0.40	1,544,856	1,532,165
Capivasertib + fulvestrant: % PD Pts receiving Capecitabine	0.333	0.27	0.40	1,532,526	1,545,111
PD utility	[redacted]			1,532,533	1,544,585
Community nurse, freq per month-PFS	1.087	0.87	1.30	1,533,023	1,544,307
Community nurse-Unit cost (PF)	1578	1284	1902	1,533,301	1,544,575
Duration_Diarrhoea	3.000	2.41	3.59	1,534,511	1,542,842
Disutilty_Diarrhoea	0.047	0.04	0.06	1,534,715	1,543,041

CT scan - thoracic & abdomen, freq per month-PFS	0.292	0.23	0.35	1,536,185	1,541,145
CT scan - thoracic & abdomen-Unit cost (PF)	2585.000	2103.26	3115.67	1,536,307	1,541,263
Duration_Hypokalaemia	3.000	2.41	3.59	1,536,200	1,541,138
Disutilty_Hypokalaemia	0.100	0.08	0.12	1,536,321	1,541,256

Figure 22. Tornado diagram



12.2.2 Probabilistic sensitivity analyses

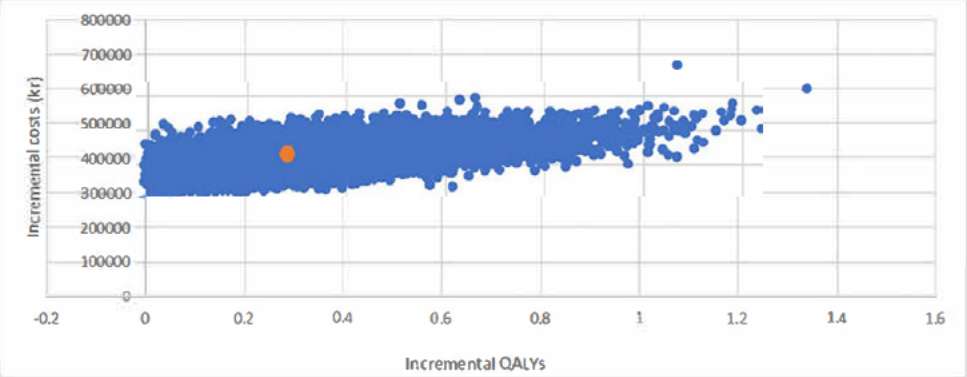
Table 62 presents the discounted mean results. Capivasertib + fulvestrant has a mean total cost of 804,617 DKK and mean total QALYs of 2.26. Fulvestrant monotherapy shows a mean total cost of 373,970 DKK and mean total QALYs of 1.91. The incremental cost per QALY for capivasertib + fulvestrant compared to fulvestrant monotherapy is 1,209,469 DKK.

Table 62. Discounted results of the probabilistic analysis

Regimen	Mean Total Costs (DKK)	Mean Total QALYs	ΔCosts	ΔQALYs	Incremental cost per QALY (DKK)
Capivasertib + fulvestrant	804,617	2.26	-	-	-
Fulvestrant monotherapy	373,970	1.91	**430,647**	**0.36**	**1,209,469**

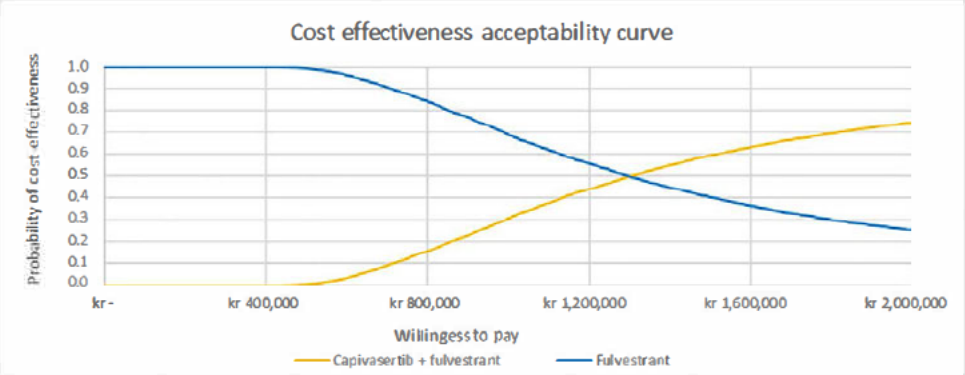
The cost-effectiveness plane (Figure 23), displays the joint uncertainty in costs and QALYs. The position of the points indicates that capivasertib + fulestrant is more costly and more effective compared to fulvestrant alone. The northeast positioning is partly shaped by the hazard adjustment incorporated in the model, which inherently assumes capivasertib plus fulvestrant is at least as effective as fulvestrant monotherapy. This methodological choice naturally guides the results towards demonstrating non-inferior or superior effectiveness.

Figure 23. Cost-effectiveness plane



The cost-effectiveness acceptability curve (Figure 24) shows that at a willingness-to-pay threshold of 1,300,000 DKK per QALY gained, the probability of capivasertib plus fulvestrant being cost-effective compared to fulvestrant monotherapy is estimated to be 50%. As the willingness-to-pay threshold increases to 2,000,000 DKK per QALY gained, this probability rises to 70%, indicating an increased likelihood of capivasertib plus fulvestrant being considered a cost-effective option.

Figure 24. Cost-effectiveness acceptability curve



13. Budget impact analysis

The budget impact analysis considers costs for pharmaceuticals, end-of-life care, adverse events, subsequent treatments, and disease management. With the introduction, annual patient numbers for the combination therapy are projected to grow from 26 to 72, capturing up to 80% market share by 2030 (Table 63, see section 3.2 for more information on the patient numbers). If capivasertib is not introduced, fulvestrant monotherapy will serve all patients, maintaining a steady number between 88 and 90 annually (Table 63). The market share for capivasertib + fulvestrant is expected to increase significantly over time, ranging from 30% to 80%. The uptake, however, will likely be gradual, as current clinical practice does not yet incorporate targeted treatments in the relevant treatment setting and practical considerations, such as routine testing for AKT pathway alterations, will need to be established within standard care procedures.

The analysis shows that recommending capivasertib results in treatment and other costs from 20,189,304 DKK in the first year to 58,023,907 DKK by the fifth year (Table 64). Consequently, the budget impact of introducing capivasertib escalates yearly, starting at 7,421,797 DKK in 2026 and reaching 28,394,414 DKK in 2030. The differences in costs between capivasertib in combination with fulvestrant versus fulvestrant monotherapy are primarily driven by higher drug acquisition costs at the list price level, prolonged treatment duration and extended patient survival. While patients on capivasertib survive longer, resulting in higher overall costs, the analysis suggests potential cost savings in disease management with capivasertib, which can offset some of the increased pharmaceutical expenses (see Health Economic model, "BIM" sheet - Disease management (End of life costs, adverse events, and (treatment specific) disease monitoring) D99:K102.

Number of patients (including assumptions of market share)

Table 63. 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		

	Year 1	Year 2	Year 3	Year 4	Year 5
Capivasertib + fulvestrant	26	44	53	62	72
Fulvestrant monotherapy	62	44	36	27	18
			Non-recommendation		
Capivasertib + fulvestrant	0	0	0	0	0
Fulvestrant monotherapy	88	88	89	89	90

Budget impact

Table 64. 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 (DKK)	20,189,304	34,225,900	43,966,420	51,450,366	58,023,901
The medicine under consideration is NOT recommended (DKK)	12,767,507	19,670,776	24,374,231	27,460,480	29,629,487
Budget impact of the recommendation (DKK)	7,421,797	14,555,124	19,592,190	23,989,886	28,394,414

14. List of experts

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Appendix A. Main characteristics of studies included

Table 65. Main characteristic of studies included

Trial name: CAPItello-291	NCT number: NCT04305496
Objective	To assesses the efficacy and safety of capivasertib–fulvestrant therapy in patients with hormone receptor–positive, HER2-negative advanced breast cancer whose disease had progressed during or after aromatase inhibitor therapy, with or without a CDK4/6 inhibitor.
Publications – title, author, journal, year	Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer, Turner, N.C. et al., N Engl J Med, 2023
Study type and design	CAPItello-291 is a Phase III, double-blind, placebo-controlled, parallel-group, randomized, multicentre study assessing the efficacy and safety of capivasertib + fulvestrant versus placebo + fulvestrant for the treatment of patients with locally advanced (inoperable) or metastatic HR+/HER2– breast cancer following recurrence or progression on or after aromatase inhibitor (AI) therapy, with or without a CDK4/6 inhibitor. The data cut-off (DCO) date for the primary analysis of PFS was 15 August 2022 (DCO1), approximately 12 months after the last patient was randomized. Primary analysis took place once PFS data had reached 77% maturity (542 PFS events) in the overall population, and 77% of PFS events had occurred in the altered population. *PIK3CA/AKT1/PTEN* mutation status, n, (%): • Known altered: 289 (40.8%) • Confirmed non-altered: 313 (44.2%) • Unknown: 106 (15.0%)
Sample size (n)	Intervention: 355 (50.1) Comparator: 353 (49.9%) No. (%) previously treated with CDK4/6 inhibitors 496 (70.1%) Overall population: including all patients with ET-resistant HR+/HER2– locally advanced (inoperable) or metastatic breast cancer Altered population: including those patients with ET-resistant HR+/HER2– locally advanced (inoperable) or metastatic breast cancer and known genetic alterations in PIK3CA, AKT1 or PTEN.
Main inclusion criteria	• Aged ≥ 18 years (≥20 years in Japan) • Pre- or postmenopausal female, or male • Histologically confirmed HR+/HER2– breast cancer • Metastatic or locally advanced disease • Disease progression during prior treatment with an AI-containing regimen • At least one lesion or bone lesion that could be accurately measured at baseline with CT or MRI • ECOG/WHO performance status of 0 or 1 with no deterioration over the previous 2 weeks, and life expectancy of ≥12 weeks

Trial name: CAPItello-291	NCT number: NCT04305496
Main exclusion criteria	• Ineligible for ET due to disease burden (e.g. life-threatening symptomatic visceral disease) • Malignancies other than breast cancer within 5 years of starting study treatment* • Radiotherapy with a wide field of radiation within 4 weeks prior to study treatment initiation, or radiotherapy with a narrow field of radiation within 2 weeks prior to study treatment initiation • Major surgery within 4 weeks prior to study treatment initiation • Unresolved toxicities from prior therapy greater than CTCAE Grade 1† at the time of study treatment initiation • Uncontrolled metastatic CNS disease • Leptomeningeal metastases • Past medical history or clinically active ILD • Clinically significant cardiac abnormalities‡ • Clinically significant abnormalities in glucose metabolism
Intervention	400 mg bid (2 tablets of 200 mg taken bid; total daily dose 800 mg) given on an intermittent weekly dosing schedule. Patients were dosed on Days 1--4 in each week of a 28-day treatment cycle. Intervention: 355 (50.1)
Comparator(s)	500 mg (2 injections) on Day 1 of Weeks 1 and 3 of cycle 1, and then on Day 1, Week 1 of each cycle thereafter. Comparator: 353 (49.9)
Follow-up time	The median follow-up time for the AKT pathway altered post CDK4/6i subgroup by endpoint and by arm (capivasertib +fulvestrant and fulvestrant alone, respectively) was: - OS DCO2: [redacted] - PFS DCO1: [redacted] - PFS2 DCO2: [redacted] - TTD DCO2 [redacted]s
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	Endpoints included in this application: **Primary endpoint:** • PFS in the overall population • PFS in the AKT pathway altered population **Secondary endpoints:** • OS: the length of time from randomization until the date of death due to any cause • PFS2: the time from randomization until second progression on next-linetreatment, as assessed by the investigator atthe local site, or death due to any cause

- ORR: the percentage of patients with at least one complete response (CR) or partial response (PR) per RECIST v1.1 criteria, as assessed by the investigator at the local site
- Duration and onset of response: the time from the date of first documented response until date of documented progression or death in the absence of disease progression
- Clinical benefit rate: the percentage of patients who a have CR, PR or stable disease (SD) per RECIST v1.1 criteria (without subsequent cancer therapy) maintained ≥ 24 weeks after randomization.
- Safety and tolerability: evaluated in terms of AEs/SAEs, vital signs, clinical chemistry/haematology/glucose metabolism parameters and electrocardiogram (ECG) parameters.
- HRQoL: Evaluation of EORTC QLQ-C30, EORTC QLQ-BR23, scale/item score, including change from baseline and time to deterioration.

Exploratory endpoints:

- Patient-reported tolerability: assessed via the patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE) and a single item on overall treatment tolerability using PGI-TT
- Time to first subsequent chemotherapy or death: time from randomization to the earlier of start date of subsequent chemotherapy after discontinuation of randomized treatment or death due to any cause
- Healthcare resource use
- Impact of treatment and disease state on health state utility: based on health state utilities derived using the EQ-5D-5L health state utility index.

Method of analysis	Analyses of the efficacy of capivasertib were based on the full analysis set (FAS) for the overall population, which included all patients randomized into the study, excluding patients randomized in China after the global cohort last patient first visit (LPFV) (see 'Data from China' below). Statistical analyses compared treatment groups based on randomized treatment, regardless of treatment actually received (the intention-to-treat principle). Therefore, patients who were randomized but were not subsequently treated were included in the FAS.[80] Efficacy analyses were also performed for the altered subgroup FAS, comprising all patients in the overall FAS with *PIK3CA/AKT1/PTEN*-altered tumours, determined by central testing (referred to as the 'altered' population). The safety analysis set (SAS) comprised all patients included in the FAS who received at least one dose of study drug (fulvestrant, capivasertib or placebo), analysed according to the treatment received. Patients who received only fulvestrant were also included in the SAS and were included in the treatment arm to which they were randomized (capivasertib or placebo). Safety analyses were also performed for the

Trial name: CAPItello-291	NCT number: NCT04305496
	altered subgroup SAS, comprising all patients in the SAS with a *PIK3CA/AKT1/PTEN*-altered tumour determined by central testing.
Subgroup analyses	See text below.
Other relevant information	N/A

Baseline characteristics for participants in the CAPItello-291 study are summarized in Table 66 (overall population and altered population) and in Table 67 (post CDK4/6 altered population – subgroup and submitted population). In the overall population, the two treatment arms were broadly balanced in terms of sex, age, race, ethnicity and disease characteristics.

In the overall population, the median age was 58 years in both the capivasertib and placebo arms, although a slightly smaller proportion of patients in the capivasertib + fulvestrant arm were <50 years of age compared to those in the placebo + fulvestrant arm (21.4% vs 28.0%). Most patients were female (99.0%) and were white (57.5%).

Demographic characteristics were also broadly balanced across treatment arms for the altered population and were consistent with the overall population.

Disease-related characteristics in the overall population were balanced between the two treatment arms. [redacted]

Overall, alterations in *PIK3CA/AKT1/PTEN* were detected in tumour samples from 289 patients (40.8%).

Table 66. Demographics and baseline characteristics

Characteristic		Overall population			Altered population		
		Capi-vasertib + fulves-trant (N=355)	Placebo + fulves-trant (N=353)	Total (N=708)	Capi-vasertib + fulves-trant (N=155)	Placebo + fulves-trant (N=134)	Total (N=289)
Age	Median, years (range)	[redacted]					
Age group (years), n (%)	<50						
	⩾50 to <65						
	⩾65to <70						
	⩾75						
Sex, n (%)	Female						
	Male						
Race/ethnic group, n (%)*	Black or African American						
	Native Hawaiian or Other Pacific Is-lander						
	American Indian or Alaskan Native						
	Asian						
	White						
	Other						
Genetic mu-tation status n (%)	Altered						
	PIK3CA only†‡						

	AKT1 only[†‡]	[redacted]
	PTEN only[†‡]	
	PIK3CA and AKT1[†]	
	PIK3CA and PTEN[†]	
	Non-altered	
	Known non-altered	
	No result (unknown)	
Disease classification	Metastatic	
	Locally advanced	
	Missing	
WHO/ECOG performance status	(0) normal activity	
	(1) restricted activity	
	(2) in bed less than or equal to 50% of the time	
AJCC Stage IV	-	
Menopausal status	Pre-/perimenopausal	
	Postmenopausal	
Receptor status	ER+/PR+	
	ER+/PR–	

	ER+/PR unknown	[redacted]
	ER–[§]	
Type of endocrine resistance	Primary	
	Secondary	
Diabetic status	Diabetes	
	No diabetes	

Notes: *Race data for Belgium, France and Hungary were not permitted to be collected per local regulations and were recorded as 'other'.†Mutually exclusive groups.‡Patients with co-occurring mutations were excluded from single gene count.
§Due to the very limited number of patients expected under this category, patients with different PR status are reported together.
Source: Clinical study report.[80]

Table 67 AKT pathway altered post CDK4/6 subgroup patient characteristics

Characteristic		AKT-altered with prior CDK4/6i Population	AKT-altered with prior CDK4/6i Population
		Capi + Fulv (N=[redacted]	Capi + Fulv (N=[redacted]
Age (years)	Median (range)	[redacted]	
Gender	Female - no. (%)		
Race	White - no. (%)		
	Asian - no. (%)		
	Black - no. (%)		
	Other - no. (%)		
Menopausal Status	Postmenopausal - no. (%)		
ECOG	PS0 - no. (%)		
	PS1 - no. (%)		
	PS2 - no. (%)		
Site of Metastases	Bone Only - no. (%)		

	Liver - no. (%)	[redacted]
	Viscera - no. (%)	
Hormone Receptor	ER+ PR+ - no. (%)	
	ER+ PR- - no. (%)	
	ER+ PR unknown - no. (%)	
Endocrine Status	Primary Resistance - no. (%)	
	Secondary Resistance - no. (%)	

Source: Data on file

Appendix B. Efficacy results per study

Results per study

The results from the CAPITello-291 trial are presented for the AKT pathway altered post CDK4/6i patient population. The results for the ITT in CAPItello-291 and the label population are presented in the publication [63].

Table 68. Results per study

Results of Capitello-291 (NCT04305496] for the AKT pathway altered post CDK4/6i patient population											
				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		
Median PFS (DCO1)	Capiverasertib + fulvestrant	[redacted]								The median PFS is based on the Kaplan-Meier estimator. The HR is based on a Cox proportional hazards model.	[Capitello-291]
	Placebo + fulvestrant										[Capitello-291]
Median OS (DCO2)	Capiverasertib + fulvestrant									The median OS is based on the Kaplan-Meier estimator. The HR is based on a Cox proportional hazards model.	[Capitello-291]
	Placebo + fulvestrant										[Capitello-291]
Median PFS2 (DCO2)	Capiverasertib + fulvestrant									The median PFS2 is based on the Kaplan-Meier estimator.	[Capitello-291]

Results of Capitello-291 (NCT04305496] for the AKT pathway altered post CDK4/6i patient population											
				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		
	Placebo + fulvestrant	[redacted]								The HR is based on a Cox proportional hazards model.	[Capitello-291]
Median TTD (DCO2)	Capiverasertib									The median TTD is based on the Kaplan-Meier estimator.	[Capitello-291]
	Fulvestrant (Capivasertib arm)										[Capitello-291]
	Fulvestrant (Placebo arm)										[Capitello-291]

Appendix C. Comparative analysis of efficacy

Not applicable

Table 69. Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

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		
N/A		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Appendix D. Extrapolation

D.1 Extrapolation of progression-free survival

D.1.1 Data input

PFS data used as data input is presented in section 6.1.4.2.

D.1.2 Model

Standard parametric models were investigated for the extrapolation of PFS based on the CAPItello-291 trial data. The following distrtributions were concidered:

- Exponential
- Weibull
- Gamma
- Log normal
- Log logistic
- Generalized gamma
- Gompertz

D.1.3 Proportional hazards

[redacted]

Figure 25. Schoenfeld residual plot – PFS

[redacted]

D.1.4 Evaluation of statistical fit (AIC and BIC)

Due to high data maturity the model selection was predominantly guided by goodness-of-fit statistics.

AIC and BIC scores are reported in Table 70 where a lower score indicates a more parsimonious fit to the CAPItello-291 trial data. The log-normal and log-logistic models consistently provided the best fit to the PFS data in CAPItello-291 and were therefore considered the primary candidate models for the base case.

Table 70. AIC and BIC values for the parametric survival models fitted to the PFS capivasertib + fulvestrant and the placebo + fulvestrant data of CAPItello-291 for the AKT pathway altered post CDK4/6i population (DCO1)

Model	Capivasertib + fulvestrant		Fulvestrant	
	AIC	BIC	AIC	BIC
Exponential	[redacted]			
Weibull				
Log-normal				
Log-logistic				
Gompertz				
Generalised gamma				
Gamma				

Abbreviations: AIC: Akaike Information Criteria; AKT: Akt Murine Thymoma Viral Oncogene; BIC: Bayesian Information Criteria; DCO: data cut-off; PFS: progression-free survival. Label populations, DCO1

D.1.5 Evaluation of visual fit

The log-normal and log-logistic models provided the best fit also visually. The fit of the models to the observed KM data is shown in Figure 26 and Figure 27.

Figure 26. Fit of the parametric survival models to the capivasertib + fulvestrant DCO1 KM data for PFS in the AKT pathway altered post CDK4/6i population in CAPItello-291

Figure 27. Fit of the parametric survival models to the placebo + fulvestrant DCO1 KM data for PFS in the AKT pathway altered post CDK4/6i population in CAPItello-291

D.1.6 Evaluation of hazard functions

A comparison of the modelled and observed smoothed hazard rates is shown in Figure 28 and Figure 29. The log-normal and log-logistic models provided the best fit also visually when assessing the hazard function. The generalised gamma model was a suitable alternative option with a plausible fit to the data.

Figure 28. Modelled and observed smoothed hazard rate for the parametric survival models to the capivasertib + fulvestrant DCO1 KM data for PFS in the AKT pathway altered post CDK4/6i population in CAPItello-291

Figure 29. Modelled and observed smoothed hazard rate for the parametric survival models to the fulvestrant DCO1 KM data for PFS in the AKT pathway altered post CDK4/6i population in CAPItello-291

D.1.7 Validation and discussion of extrapolated curves

The estimated mean and median PFS for capivasertib + fulvestrant and fulvestrant monotherapy are presented in Table 71. There is limited external data assessing 2L mBC treatments, including fulvestrant, in the post CDK4/6i setting. Some evidence indicates that 2L fulvestrant treated patients post CDK4/6i experience approximately 2-3 months PFS (as presented in section 3.3). Thus, the CAPItello-291 trial data was mainly used for the validation of extrapolations since it includes the relevant patient population (post CDK4/6i).

For fulvestrant monotherapy, the log-normal, log-logistic and generalized gamma models (identified through the statistical and visual fit assessments) produced mean and median PFS estimates that are in line with the reported estimates from the CAPItello-291 trial. This is also true for the median PFS for capivasertib + fulvestrant that was reached between month five and six in the health economic model.

The reported median and RMST PFS for fulvestrant monotherapy are [redacted] respectively. The extrapolated mean PFS based on the log normal distribution [redacted] is well aligned with the reported RMST. The extrapolated median PFS [redacted] is close to the reported median PFS (2 months), and it is aligned with external evidence [redacted]

With approximately [redacted] of patients still progression free at the first data cut in the capivasertib + fulvestrant arm, the mean PFS was expected to be longer compared to reported mean PFS [redacted] when extrapolated. The log normal generates the most plausible mean PFS estimate of [redacted] months compared to the other two models [redacted]

Table 71. Estimated progression-free survival for capivasertib + fulvestrant and fulvestrant monotherapy

Treatment	Mean PFS (months)	Median PFS (months)
Log normal		
Capivasertib + fulvestrant	[redacted]	
Fulvestrant monotherapy		
Log logistic		
Capivasertib + fulvestrant	[redacted]	
Fulvestrant monotherapy		
Generalized gamma		
Capivasertib + fulvestrant	[redacted]	
Fulvestrant monotherapy		

	CAPItello-291
Capivasertib + fulvestrant	[redacted]
Fulvestrant monotherapy	

Abbreviations: PFS, Progression-free survival *The restricted mean survival time calculation uses a cut-off value of [redacted] This is the smallest value among the largest observed times across the treatment groups.

In line with the guidelines and due to the lack of external data, the goodness-of-fit statistics, the visual fit and reported mean and median PFS values from the CAPItello-291 were used for model selection. Based on these factors, the log normal model produces clinically plausible estimates and was therefore considered most suitable. As both treatments are ET-based regimens, it was assumed that the course of disease progression follows similar trends (i.e., similar hazard functions). Using the same parametric function to extrapolate PFS was therefore considered clinically plausible.

The log-logistic and generalized gamma models were explored in scenario analyses.

D.1.8 Adjustment of background mortality

Background mortality was implemented in line with the DMC guidance, using the proposed addendum to the health economic model [85].

D.1.9 Adjustment for treatment switching/cross-over

No cross-over adjustments were applied for PFS.

D.1.10 Waning effect

No waning effect was applied for PFS.

D.1.11 Cure-point

No cure point was applied for PFS.

D.2 Extrapolation of overall survival

D.2.1 Data input

OS data used as data input is presented in section 6.1.4.3.

D.2.2 Model

Standard parametric models were investigated for the extrapolation of OS based on the CAPItello-291 trial data. The following distrtributions were concidered:

- Exponential
- Weibull
- Gamma
- Log normal
- Log logistic
- Generalized gamma
- Gompertz

D.2.3 Proportional hazards

[redacted]However, given the biological plausibility and the course of disease for patients receiving ET-based regimens, similar patterns of disease advancement, remission and death are expected, particularly in the long term (see section 8.4). [redacted]

It was therefore of interest to identify a hazard function that reflects the course of the disease additionally to the two treatment arms. The same parametric distributions were fitted to each treatment arm independently but assessed jointly.

Figure 30. Schoenfeld residual plot - OS

[redacted]

D.2.4 Evaluation of statistical fit

The AIC and BIC values are comparable (Table 72), with only minor differences among the various functions. As a result, no function can be definitively excluded.

Table 72. AIC and BIC values for the parametric survival models fitted to the OS capivasertib + fulvestrant and the placebo + fulvestrant data of CAPItello-291 (AKT pathway altered post CDK4/6i; DCO2)

Model	Capivasertib + fulvestrant		Fulvestrant	
	AIC	BIC	AIC	BIC
Exponential	[redacted]			
Weibull				
Log-normal				
Log-logistic				
Gompertz				
Generalised gamma				
Gamma				

Abbreviations: AIC: Akaike Information Criteria; AKT: Akt Murine Thymoma Viral Oncogene; BIC: Bayesian Information Criteria; DCO: data cut-off; PFS: progression-free survival.

D.2.5 Evaluation of visual fit

The visual fit of the different parametric models to the KM curves for capivasertib + fulvestrant and fulvestrant monotherapy, respectively, are presented in Figure 31.

Most distributions seem to fit, capturing the KM data for both treatments until [redacted]. When evaluating the visual fit for both arms simultaneously, the [redacted]. Based on the fit to the KM data no other function can be definitively excluded. The inclusion of the hazard function assessment, landmark survival analysis, and external data is necessary for the model selection process.

Figure 31. KM curve and parametric models – Capivasertib + fulvestrant and fulvestrant monotherapy – DCO2 OS

D.2.6 Evaluation of hazard functions

For the evaluation of hazard function, visual fit and clinical/ biological plausibility were assessed.

The visual fit of the different parametric models to the smoothed hazard functions for capivasertib + fulvestrant and fulvestrant monotherapy, respectively, are presented in Figure 32.[redacted] (see Figure 8 for number of patients at risk at various time points).

[redacted]

Figure 32. Smoothed hazard and parametric models – Capivasertib + fulvestrant and fulvestrant monotherapy – DCO2 OS

D.2.7 Validation and discussion of extrapolated curves

To validate the choice of model for OS extrapolations, both post-progression survival and OS landmark estimates were assessed.

It is anticipated that

When considering post-progression survival after 2L treatments (i.e., capivasertib+fulvestrant and fulvestrant alone) as predicted by parametric models, the gamma distribution suggests comparable outcomes ( ). Other parametric models, such as Weibull and Gompertz, predict longer post-progression survival for fulvestrant alone ( ) and increased (Table 73) compared to capivasertib + fulvestrant, which is not considered clinically plausible.

. This indicates that the gamma distribution

reflects the disease course if aligning with the expectations that, [redacted]

Table 73. OS landmark survival probabilities predicted by each parametric model – with hazard adjustment (AKT pathway altered post CDK4/6i population)

Model	Years					
	1	2	3	5	10	20
Capivasertib + fulvestrant						
Observed (KM, DCO2)	[redacted]					
Weibull						
Gompertz						
Gamma						
Fulvest						
Observed (KM, DCO2)	[redacted]					
Weibull						
Gompertz						
Gamma						

Abbreviations: CDK4/6i: cyclin-dependent kinase 4 and 6 inhibitor; KM: Kaplan-Meier; OS: overall survival

Table 74. OS landmark survival probabilities predicted by each parametric model – without hazard adjustment (AKT pathway altered post CDK4/6i population)

Model	Years					
	1	2	3	5	10	20
Capivasertib + fulvestrant						
Observed (KM, DCO2)	[redacted]					
Weibull						
Gompertz						
Gamma						
Fulvestrant monotherapy						
Observed (KM, DCO2)	[redacted]					
Weibull						
Gompertz						
Gamma						

Abbreviations: CDK4/6i: cyclin-dependent kinase 4 and 6 inhibitor; KM: Kaplan-Meier; OS: overall survival

Figure 33 shows the OS KM data for fulvestrant + placebo from the CAPItello-291 trial, the real-world OS KM data for patients that receive 2L fulvestrant monotherapy after 1L CDK4/6i+ET in Denmark (see Appendix K), as well as the extrapolation of CAPITello-291 OS based on the gamma distribution for fulvestrant. [redacted]

Figure 33. Overall survival – Fulvestrant monotherapy CAPItello-291 and Danish clinical practice (see Appendix K)

[redacted]

As mentioned, there is a lack of data for mBC patients that were previously exposed to CDK4/6i. However, long-term OS data for HR+/HER2- mBC shows that there are long term survivors with mBC (up to 20 years from diagnosis) [93, 94]. A Swedish registry study showed long-term survival up to 200 months and beyond (Figure 34) [93]. A similar survival outcome was observed in data from the Norwegian national quality register for breast cancer, with approximately 20% of HR+/HER2- patients diagnosed with mBC alive 10 years from diagnosis (Figure 35) [95].

Even though the data shows OS from diagnosis rather than specifically from 2L treatment initiation, and despite the heterogeneity of the real-world patient population, a small proportion of patients receiving 2L treatment in a metastatic setting are expected to survive 10 years or longer from treatment initiation.

With landmark OS estimates of [redacted]), the gamma model produces the most reasonable long-term OS for capivasertib + fulvestrant and fulvestrant monotherapy for patients with AKT pathway altered post CDK4/6i mBC receiving 2L treatment.

Figure 34. Overall survival from metastatic breast cancer diagnosis stratified by hormone receptor status based on Swedish national registry data [93].

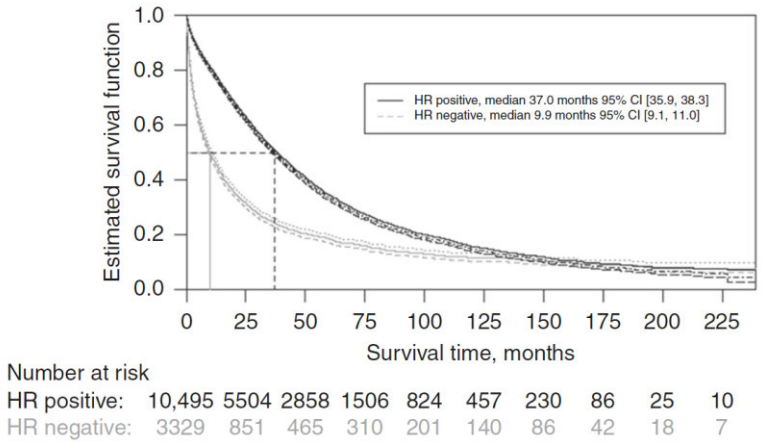
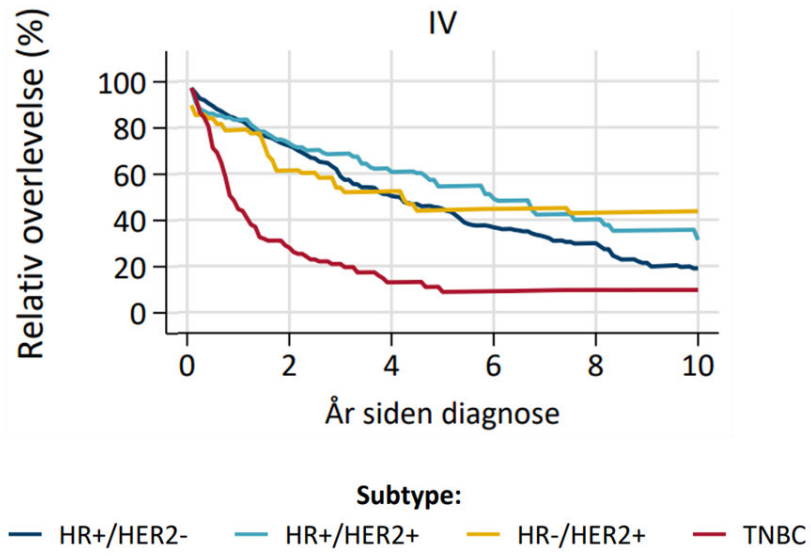


Figure 35. Estimated relative survival 10 years from diagnosis of metastatic breast cancer (stadium IV) by subtype 2019-2023 from the Norwegian national quality register for breast cancer [95].



D.2.8 Adjustment of background mortality

Background mortality was implemented in line with the DMC guidance, using the proposed addendum to the health economic model [85].

D.2.9 Adjustment for treatment switching/ cross-over

Not applicable

D.2.10 Waning effect

See section 8.4.

D.2.11 Cure-point

Not applicable

D.3 Extrapolation of time to treatment discontinuation

D.3.1 Data input

TTD data used as data input is presented in section 6.1.4.5.

It was assumed that patients terminate treatment upon disease progression. Therefore, TTD is limited by PFS in the health economic model. In other words, the TTD curve cannot exceed PFS. PFS is presented in section 6.1.4.2.

D.3.2 Model

Standard parametric models were investigated for the extrapolation of TTD based on the CAPItello-291 trial data. The following distrtributions were concidered:

- Exponential
- Weibull
- Gamma
- Log normal
- Log logistic
- Generalized gamma
- Gompertz

D.3.3 Proportional hazards

Based on the diagnostic plots, the PH assumption was violated for TTD and only independent parametric models were considered (Figure 36).

Figure 36. Schoenfeld residual plot - TTD

D.3.4 Evaluation of statistical fit

The goodness-of-fit statistics for TTD for capivasertib are presented in Table 75. Based on the AIC and BIC values, the lognormal and loglogistic distributions are the best fitting models. The loglogistic distribution is also the best fitting model for fulvestrant (both for the capivasertib + fulvestrant and the placebo + fulvestrant arms).

Table 75. AIC and BIC values - Capivasertib DCO2 TTD – AKT pathway altered post CDK4/6i

Distribution	AIC	BIC
Exponential		
Weibull		
Log-normal		
Log-logistic		
Gompertz		
Generalised Gamma		
Gamma		

Table 76. AIC and BIC values - for fulvestrant in the capivasertib + fulvestrant arm and fulvestrant in the placebo + fulvestrant arm DCO2 TTD – AKT pathway altered post CDK4/6i

Distribution	Fulvestrant in Placebo + Fulvestrant arm		Fulvestrant in Capivasertib + Fulvestrant arm	
	AIC	BIC	AIC	BIC
Exponential		[redacted]		
Weibull				
Log-normal				
Log-logistic				
Gompertz				
Generalised Gamma				
Gamma				

D.3.5 Evaluation of visual fit

The visual fit of the parametric distributions to the TTD KM curves and smoothed hazards are presented below for capivasertib (Figure 37 and Figure 39) and fulvestrant (both for the capivasertib + fulvestrant and the placebo + fulvestrant arms) (Figure 38 and Figure 40).

Figure 37. KM curves and parametric models – Capivasertib and placebo – DCO2 TTD AKT pathway altered post CDK4/6i

Figure 38. KM curves and parametric models – fulvestrant in the capivasertib + fulvestrant arm and fulvestrant in the placebo + fulvestrant arm – DCO2 TTD AKT pathway altered post CDK4/6i

Figure 39. Smoothed hazard and parametric models – Capivasertib and placebo – DCO2 TTD AKT pathway altered post CDK4/6i

Figure 40. Smoothed hazard and parametric models – fulvestrant in the capivasertib + fulvestrant arm and fulvestrant in the placebo + fulvestrant arm – DCO2 TTD AKT pathway altered post CDK4/6i

D.3.6 Evaluation of hazard function

The hazard function as assessed as part of the visual assessment, see section D.3.5.

D.3.7 Validation and discussion of extrapolated curves

In line with the high degree of data maturity, the log logistic distribution is used to extrapolate TTD for fulvestrant (alone and as part of the capivasertib + fulvestrant combination) and capivasertib.

D.3.8 Adjustment of background mortality

Not applied. However, in the model TTD cannot exceed PFS. For PFS background mortality was applied.

D.3.9 Adjustment for treatment switching/ cross-over

Not applicable.

D.3.10 Waning effect

Not applicable.

D.3.11 Cure-point

Not applicable.

Appendix E. Serious adverse events

Incidence and management of SAEs

At DCO1, [redacted] The most frequently reported SAEs were diarrhoea, rash maculopapular and vomiting (Table 77).

Table 77. SAEs reported in two or more patients in either treatment arm (SAS)

	Number (%) of patients*	
MedDRA preferred term	**Capivasertib + fulvestrant (N=355)**	**Placebo + fulvestrant (N=350)**
Patients with any SAE	[redacted]	
Diarrhoea		
Rash maculopapular†		
Vomiting		
Acute kidney injury		
Hyperglycaemia		
Asthenia		
Pneumonia aspiration		
Sepsis		
Hypercalcaemia		
Nausea		
Platelet count decreased		

Notes: *The number (%) of patients with AEs, sorted by preferred term in order of descending frequency of occurrence in the capivasertib + fulvestrant arm.
†Serious AEs of rash as an AESI grouped term (including rash, rash macular, rash maculopapular, rash popular, and rash pruritic) were reported at an incidence of [redacted] in the capivasertib + fulvestrant arm, and [redacted] in the placebo + fulvestrant arm
Patients with multiple SAEs are counted once for each system organ class/preferred term
Note: SAEs with an onset date on/after date of first dose; SAEs with onset date prior to dosing which worsen after dosing; SAE occurring up to 30 days (+ 7 days) following date of last dose are reported.

MedDRA version 25.0
Abbreviations: AESI, adverse event of special interest; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; SAS, safety analysis set.
Source: Clinical study report.[80]

Appendix F. Health-related quality of life

F.1 Background

Quality of life was assessed within CAPI-291 using the EQ-5D-5L. The assessment schedule for EQ-5D-5L in CAPI-291 is available from the clinical study protocol. This report details the analysis of Danish utility values derived from the EQ-5D-5L profiles in CAPI-291 using the 5L Danish value set by Jensen et al [86].

The EQ-5D is a standardised measure of self-reported health, developed by the EuroQol Group. There are 5 dimensions or domains: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. In the 5-level ('5L') version of the questionnaire, there are 5 possible levels of response that a subject can give for each dimension: no, mild, moderate, severe, and severe / unable to.

An EQ-5D profile consists of a 5-digit value, with each digit representing a subject's response for each domain. The EQ-5D profiles can be converted to a health state utilities using country-specific value sets that are reflective of the country of interest. The maximum health state utility value is 1, which represents 'full health'. A value of 0 corresponds to a quality of life equivalent to being dead, and negative values are possible which represent a quality of life worse than death.

F.2 Methods

A descriptive summary of the EQ-5D health state utilities by arm and study visit, and by arm and treatment discontinuation status is provided in the results section. The summary analysis includes estimates of mean, standard deviations, median, and interquartile range (IQR) of utility scores in the full analysis set (FAS) analysis set of CAPItello-291, consisting of all completed EQ-5D-5L measures (excluding EQ-5D-5L with any missing domain responses).

The statistical relationship between EQ-5D-5L health state utility and treatment, and health status was assessed using regression analysis. To account for the repeated measurements in the study, a mixed model for repeated measures (MMRM) method was used to model EQ-5D-5L health state utilities. The MMRM analysis was performed on a dataset excluding any observations recorded after the time of censoring for progression. Due to censoring, the EQ-5D-5L observations obtained during this period have an unknown/missing health status and therefore, must be omitted from the analysis.

The MMRM analysis was performed using the restricted maximum likelihood method (REML) with the following covariates included as fixed effects:

- [redacted]

The correlation of repeated utility measurements within subjects over time was captured via the specification of covariance structures for the MMRM. This report presents the results from the models using the first covariance structure in the sequence that successfully converged for all models (i.e., for each of the 4 covariate options). If for a particular set of covariates none of the models converged, then no results are presented for that model, and the remaining model results are based on the most flexible covariance structure for which the models converged.

The hierarchy of covariance structures tested, in order of most to least flexible, is shown below:

1. Unstructured – each visit is allowed to have a different variance, and each combination of visits is allowed to have a different covariance.
2. Toeplitz with heterogeneity – each visit is allowed to have a different variance, covariances between measurements depend on how many visits apart they are.
3. Autoregressive, order 1 (AR(1)) with heterogeneity – each visit is allowed to have a different variance, and covariances decrease based on how many visits apart they are. Covariances decrease towards zero as the number of visits between observations increases.
4. Toeplitz – as above for number 2, but each visit shares the same variance.
5. Autoregression, order 1 (AR(1)) – as above for number 3, but each visit shares the same variance.

For each model, parameter estimates, and marginal ('least square') means are presented including 95% confidence intervals.

The marginal ('least square') mean provides a model-based estimate of the mean utility score by status (treatment and/or Treatment discontinuation status) that is averaged over observations and with adjustment for repeated measures. The estimated marginal mean and its associated standard error or confidence interval can be used as utility inputs to the global cost-effectiveness model.

All regression output is saved as a spreadsheet file including covariance matrices for the parameters. Confidence intervals are based on robust standard error estimates.

F.3 Results - Descriptive analysis

In total, [redacted] EQ-5D-5L observations were available from [redacted] patients. Of these, [redacted] observations were recorded pre-discontinuation, [redacted] were recorded post-discontinuation and [redacted] were recorded after censoring for treatment discontinuation.

Table 78. Pattern of missing data and completion

Time point	Treatment group	Expected[a]	Received[b]	Evaluable[c]	Compliance rate (%)[d]	Evaluability rate (%)[e]
Overall	Capi + Fulv	[redacted]				
	Pbo + Fulv					
Baseline	Capi + Fulv					
	Pbo + Fulv					
Cycle 2 Week 1 Day 1	Capi + Fulv					
	Pbo + Fulv					
Cycle 3 Week 1 Day 1	Capi + Fulv					
	Pbo + Fulv					
Cycle 4 Week 1 Day 1	Capi + Fulv					
	Pbo + Fulv					
Cycle 5 Week 1 Day 1	Capi + Fulv					
	Pbo + Fulv					
Cycle 6 Week 1 Day 1	Capi + Fulv					
	Pbo + Fulv					
Cycle 7 Week 1 Day 1	Capi + Fulv					
	Pbo + Fulv					
Cycle 8 Week 1 Day 1	Capi + Fulv					
	Pbo + Fulv					
Cycle 9 Week 1 Day 1	Capi + Fulv					
	Pbo + Fulv					
Cycle 10 Week 1 Day 1	Capi + Fulv					
	Pbo + Fulv					
	Capi + Fulv					

Cycle 11 Week 1 Day 1	Pbo + Fulv	[redacted]
Cycle 12 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	
Cycle 13 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	
Cycle 14 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	
Cycle 15 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	
Cycle 16 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	
Cycle 17 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	
Cycle 18 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	
Cycle 19 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	
Cycle 20 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	
Cycle 21 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	
Cycle 22 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	
Cycle 23 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	

Cycle 24 Week 1 Day 1	Capi + Fulv	[redacted]
	Pbo + Fulv	
Cycle 25 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	
Cycle 26 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	
Cycle 27 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	
Cycle 28 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	
Cycle 29 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	
Cycle 30 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	
Cycle 31 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	
Cycle 32 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	
Cycle 33 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	
Cycle 34 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	
Cycle 35 Week 1 Day 1	Capi + Fulv	
	Pbo + Fulv	
	Capi + Fulv	

Cycle 36 Week 1 Day 1	Pbo + Fulv	[redacted]
Cycle 37 Week 1	Capi + Fulv	
Day 1	Pbo + Fulv	
Cycle 38 Week 1	Capi + Fulv	
Day 1	Pbo + Fulv	
Cycle 39 Week 1	Capi + Fulv	
Day 1	Pbo + Fulv	

Abbreviations: Capi, capivasertiv; Fulv, fulvestrant; Pbo, Placebo. In the overall row, patients are counted as Received/Evaluable if they have a Received/Evaluable baseline and at least one Received/Evaluable post-baseline form. Time points are reported by visit for each treatment group, provided at least one group has ≥ 20 patients with data at a given visit

[a]Number of patients who has not withdrawn from the study at given time point

Figure 41. Observation per visit

[redacted]

Table 79. Utility summary statistics

Treatment	Scenario	Subjects	Observations	Mean (SD)	Median (IQR)	Min	Max
Placebo + Fulvestrant	[redacted]						
Capivasertib + Fulvestrant							
Placebo + Fulvestrant							
Capivasertib + Fulvestrant							
Pooled treatments							
Pooled treatments							
Placebo + Fulvestrant							
Placebo + Fulvestrant							
Capivasertib + Fulvestrant							
Capivasertib + Fulvestrant							
Placebo + Fulvestrant							
Capivasertib + Fulvestrant							

F.4 Results - Regression analysis

The results presented in this section were generated from MMRMs with the following covariance structure: Autoregressive - order 1.

Table 80. Goodness of fit

Description	converges	AIC	BIC
[redacted]			

The best fitting model in terms of AIC was the model including a term for Treatment discontinuation status.

F.5 Results - Summary of Statistical fits

The following tables contain summaries of the point estimates and marginal means produced from each model.

F.5.1 Point Estimates

Table 81. Summary of point estimates

Parameter	Treatment	Treatment discontinuation status	Treatment + Treatment discontinuation status	Treatment * Treatment discontinuation status
[redacted]				

F.5.2 Marginal Means

Table 82. Summary of marginal means

Parameter	Treatment	Treatment discontinuation status	Treatment + Treatment discontinuation status	Treatment * Treatment discontinuation status
[redacted]				

F.6 Model fits:

F.6.1 Model terms: Treatment

Table 83. Parameter Estimates

Parameter	Estimate	SE	DF	p_value	95% LCL	95% UCL
[redacted]						

Table 84. Marginal means

TRT01P	Estimate	SE	DF	95% LCL	95% UCL
[redacted]					

F.6.2 Model terms: Treatment discontinuation status

Table 85. Parameter Estimates

Parameter	Estimate	SE	DF	p_value	95% LCL	95% UCL
[redacted]						

Table 86. Marginal means

TDFL	Estimate	SE	DF	95% LCL	95% UCL
[redacted]					

F.6.3 Model terms: Treatment + Treatment discontinuation status

Table 87. Parameter Estimates

Parameter	Estimate	SE	DF	p_value	95% LCL	95% UCL
[redacted]						

Table 88. Marginal means

TRT01P	TDFL	Estimate	SE	DF	95% LCL	95% UCL
[redacted]						

F.6.4 Model terms: Treatment * Treatment discontinuation status

Table 89. Parameter Estimates

Parameter	Estimate	SE	DF	p_value	95% LCL	95% UCL
[redacted]						

Table 90. Marginal means

TRT01P	TDFL	Estimate	SE	DF	95% LCL	95% UCL
[redacted]						

Appendix G. Probabilistic sensitivity analyses

Table 91 shows the data/assumptions (point estimate, and lower and upper bound) form the basis for the selected probability distributions used in the probabilistic analysis. For parametric survival models, Cholesky decomposition was used to account for uncertainty in model parameters and their correlations (see ”Parameter sheet”, A177:AN251).

Table 91. Overview of parameters in the PSA

Variable	Input	Std Error	lower	upper	Distribution	α	β
Discount rate							
Discount rate_Costs	0.035	0.0035	0.03	0.042	Beta	96.47	2659.67
Discount rate_QALYs	0.035	0.0035	0.03	0.042	Beta	96.47	2659.67
Patient characteristics							
Starting Age, years	[redacted]				Normal	[redacted]	
Average body weight							
Male					Normal		
Female					Normal		
Body surface area							
Male					Normal		
Female					Normal		
Disease management							
Progression-free							
Oncology consultant office, freq per month-PFS	0.362	0.036	0.291	0.43	Normal	0.362	0.036
Community nurse, freq per month-PFS	1.087	1.087	0.873	1.30	Normal	1.087	0.109
Clinical nurse specialist, freq per month-PFS	0.362	0.036	0.291	0.43	Normal	0.362	0.036
CT scan - thoracic & abdomen, freq per month-PFS	0.292	0.029	0.235	0.35	Normal	0.292	0.029
Blood test (Full blood count), freq per month-PFS	0.292	0.029	0.235	0.35	Normal	0.292	0.029
Oncology consultant office, % of pts - PFS	100%	10%	0.804	1.20	Normal	1	0.1

Community nurse, % of pts - PFS	100%	10%	0.804	1.20	Normal	1	0.1
Clinical nurse specialist, % of pts - PFS	100%	10%	0.804	1.20	Normal	1	0.1
CT scan - thoracic & abdomen, % of pts - PFS	100%	10%	0.804	1.20	Normal	1	0.1
MRI, % of pts - PFS	100%	10%	0.804	1.20	Normal	1	0.1
Blood test (Full blood count), % of pts - PFS	100%	10%	0.804	1.20	Normal	1	0.1
Progressed disease							
Oncology consultant office, freq per month-PD	0.40	0.04	0.32	0.47	Normal	0.395	0.040
Community nurse, freq per month-PD	0.36	0.04	0.29	0.43	Normal	0.362	0.036
Clinical nurse specialist, freq per month-PD	1.45	0.15	1.17	1.73	Normal	1.449	0.145
CT scan - thoracic & abdomen, freq per month-PD	0.29	0.03	0.23	0.35	Normal	0.292	0.029
MRI, freq per month-PD	0.00	0.00	0.00	0.00	Normal	0.000	0.000
Blood test (Full blood count), freq per month-PD	1.45	0.15	1.17	1.73	Normal	1.449	0.145
Oncology consultant office, % of pts - PD	1	0.1	0.80	1.20	Normal	1	0.1
Community nurse, % of pts - PD	1	0.1	0.80	1.20	Normal	1	0.1
Clinical nurse specialist, % of pts - PD	1	0.1	0.80	1.20	Normal	1	0.1
CT scan - thoracic & abdomen, % of pts - PD	1	0.1	0.80	1.20	Normal	1	0.1
MRI, % of pts - PD	1	0.1	0.80	1.20	Normal	1	0.1
Blood test (Full blood count), % of pts - PD	1	0.1	0.80	1.20	Normal	1	0.1
Unit costs - Progression free							
Oncology consultant office-Unit cost (PF)	1578	157.8	1283.92	1901.95	Gamma	100	15.78
Community nurse-Unit cost (PF)	1578	157.8	1283.92	1901.95	Gamma	100	15.78

Clinical nurse specialist-Unit cost (PF)	1578	157.8	1283.92	1901.95	Gamma	100	15.78
CT scan - thoracic & abdomen-Unit cost (PF)	2701	270.1	1283.92	1901.95	Gamma	100	27.01
MRI-Unit cost (PF)	2701	270.1	1283.92	1901.95	Gamma	100	27.01
Blood test (Full blood count)-Unit cost (PF)	1578	157.8	1283.92	1901.95	Gamma	100	15.78
Unit costs - Progressed disease							
Oncology consultant office-Unit cost (PD)	1578	157.8	1283.92	1901.95	Gamma	100	15.78
Community nurse-Unit cost (PD)	1578	157.8	1283.92	1901.95	Gamma	100	15.78
Clinical nurse specialist-Unit cost (PD)	1578	157.8	1283.92	1901.95	Gamma	100	15.78
CT scan - thoracic & abdomen-Unit cost (PD)	2701	270.1	2197.64	3255.49	Gamma	100	27.01
MRI-Unit cost (PD)	2701	270.1	2197.64	3255.49	Gamma	100	27.01
Blood test (Full blood count)-Unit cost (PD)	1578	157.8	1283.92	1901.95	Gamma	100	15.78
HSUV	[redacted]						
PFS utility					Beta		
PFS utility 95% LCI							
PFS utility 95% UCI							
PD utility					Beta		
PD utility 95% LCI							
PD utility 95% UCI							
Disutilities							
Disutilty_Diarrhoea	0.0468	0.00468	0.038	0.056	Gamma	100	0.000468
Disutilty_Rash maculo-papular	0.03248	0.003248	0.026	0.039	Gamma	100	0.000325

Disutilty_Rash	0.03248	0.003248	0.026	0.039	Gamma	100	0.000325
Disutilty_Hyperglycaemia	0.09	0.009	0.073	0.11	Gamma	100	0.0009
Disutilty_Hypokalaemia	0.1	0.01	0.081	0.12	Gamma	100	0.001
Disutilty_Anaemia	0.119	0.0119	0.097	0.14	Gamma	100	0.00119
Disutilty_Stomatitis	0.151	0.0151	0.122	0.18	Gamma	100	0.00151
Duration_Diarrhoea	3	0.3	2.41	3.58	Normal	3	0.3
Duration_Rash maculo-papular	3	0.3	2.41	3.58	Normal	3	0.3
Duration_Rash	3	0.3	2.41	3.58	Normal	3	0.3
Duration_Hyperglycaemia	3	0.3	2.41	3.58	Normal	3	0.3
Duration_Hypokalaemia	3	0.3	2.41	3.58	Normal	3	0.3
Duration_Anaemia	3	0.3	2.41	3.58	Normal	3	0.3
Duration_Aspartate aminotransferase increased	3	0.3	2.41	3.58	Normal	3	0.3
Duration_Alanine aminotransferase increased	3	0.3	2.41	3.58	Normal	3	0.3
Duration_Stomatitis	3	0.3	2.41	3.58	Normal	3	0.3
Safety							
Diarrhoea events: Capivasertib + fulvestrant	[redacted]				Gamma	[redacted]	
Rash maculo-papular events: Capivasertib + fulvestrant					Gamma		
Rash events: Capivasertib + fulvestrant					Gamma		
Hyperglycaemia events: Capivasertib + fulvestrant					Gamma		
Hypokalaemia events: Capivasertib + fulvestrant					Gamma		
Anaemia events: Capivasertib + fulvestrant					Gamma		

Aspartate aminotransferase increased events: Capivasertib + fulvestrant	[redacted]	Gamma	[redacted]
Alanine aminotransferase increased events: Capivasertib + fulvestrant		Gamma	
Stomatitis events: Capivasertib + fulvestrant		Gamma	
Diarrhoea events: Fulvestrant		Gamma	
Rash maculo-papular events: Fulvestrant		Gamma	
Rash events: Fulvestrant		Gamma	
Hyperglycaemia events: Fulvestrant		Gamma	
Hypokalaemia events: Fulvestrant		Gamma	
Anaemia events: Fulvestrant		Gamma	
Aspartate aminotransferase increased events: Fulvestrant		Gamma	
Alanine aminotransferase increased events: Fulvestrant		Gamma	
Stomatitis events: Fulvestrant		Gamma	
Adverse evnnts costs			
Diarrhoea		Gamma	
Rash maculo-papular		Gamma	
Rash		Gamma	
Hyperglycaemia		Gamma	
Hypokalaemia		Gamma	
Anaemia		Gamma	
Aspartate aminotransferase increased		Gamma	
Alanine aminotransferase increased		Gamma	

Stomatitis	[redacted]				Gamma		[redacted]
End of life cost					Gamma		
Drug costs							
Capivasertib + fulvestrant							
Capivasertib - RDI					Beta		
fulvestrant (1st 4 weeks) - RDI					Beta		
fulvestrant (post 4 weeks) - RDI					Beta		
Fulvestrant							
Fulvestrant (1st 4 weeks) - RDI					Beta		
Fulvestrant (post 4 weeks) - RDI					Beta		
Treatment specific monitoring							
Total Treatment specific monitoring costs for capivasertib per month (kr)	15.6	1.56	12.69	18.80	Gamma	100	0.156
One off cost - fasting glucose at treatment initiation for week 2 and 6 of treatment (kr)	18	1.8	14.64	21.69521	Gamma	100	0.18
Drug wastage – capivasertib + fulvestrant							
Proportion of patients with dose reduction leading to wastage	0.30	0.03	0.24	0.36	Gamma	100.00	0.00
Patient costs							
Disease management - duration							
Oncology consultant office	1	0.1	0.8	1.196	Normal	1	0.1
Clinical nurse specialist	1	0.1	0.8	1.196	Normal	1	0.1
CT scan - thoracic & abdomen	1	0.1	0.8	1.196	Normal	1	0.1
AE management - duration							

AE visit duration	72.00	7.20	57.89	86.11	Normal	72.00	7.20
AE leading to hospitalization, %							
Capivasertib: Diarrhea					Beta		
Capivasertib: Rash					Beta		
Capivasertib: Hyperglycemia					Beta		
Fulvestrant: Diarrhea					Beta		
Fulvestrant: Rash					Beta		
Fulvestrant: Hyperglycemia					Beta		
PFS							
Frequency - Oncology consultant office	0.362	0.036	0.29	0.43	Normal	0.362351	0.036235
Frequency - Clinical nurse specialist	0.362	0.036	0.29	0.43	Normal	0.362351	0.036235
Frequency - CT scan - thoracic & abdomen	0.292	0.029	0.23	0.35	Normal	0.291667	0.029167
PD							
Frequency - Oncology consultant office	0.395	0.04	0.31	0.47	Normal	0.395292	0.039529
Frequency - Clinical nurse specialist	1.449	0.145	1.16	1.73	Normal	1.449405	0.14494
Frequency - CT scan - thoracic & abdomen	0.292	0.029	0.23	0.35	Normal	0.291667	0.029167
Unit cost - patient cost							
Transportation (round trip)	144	14.4	117.16	173.56	Gamma	100	1.44
Patient time (1h)	188	18.8	152.96	226.59	Gamma	100	1.88
Total patient cost - PFS							
Disease management	601.50	60.15	489.41	724.99	Gamma	100.00	6.02

Total patient cost - PD							
Disease management	732.74	73.27	596.19	883.16	Gamma	100.00	7.33
Total patient costs - AE							
AE management - Capivasertib + fulvestrant	615.60	61.56	500.88	741.98	Gamma	100.00	6.16
AE management - fulvestrant	41.04	4.10	33.39	49.47	Gamma	100.00	0.41
Subsequent treatment	[redacted]						
Capivasertib + fulvestrant: % PD Pts receiving Any subsequent Tx					Beta	[redacted]	
Capivasertib + fulvestrant: % PD Pts receiving Cytotoxic chemotherapy					Beta		
Fulvestrant: % PD Pts receiving Any subsequent Tx					Beta		
Fulvestrant: % PD Pts receiving Cytotoxic chemotherapy					Beta		
Capivasertib + fulvestrant: % PD Pts receiving Capecitabine					Beta		
Capivasertib + fulvestrant: % PD Pts receiving Eribulin					Beta		
Capivasertib + fulvestrant: % PD Pts receiving Paclitaxel					Beta		
Fulvestrant: % PD Pts receiving Capecitabine					Beta		
Fulvestrant: % PD Pts receiving Eribulin					Beta		
Fulvestrant: % PD Pts receiving Paclitaxel					Beta		
Duration (months): Capecitabine					Normal		
Duration (months): Eribulin					Normal		
Duration (months): Paclitaxel					Normal		
Cost per month: Capecitabine					Gamma		
Cost per month: Eribulin					Gamma		

Cost per month: Paclitaxel	7268.02	726.80	5913.55	8760.07	Gamma	100.00	72.68
Cost per administration: IV	1578.00	157.80	1283.92	1901.95	Gamma	100.00	15.78
Capivasertib + fulvestrant: Sub Tx cost_Cytotoxic chemotherapy	60092.83	6009.28	48893.92	72429.25	Gamma	100.00	600.93
Capivasertib + fulvestrant: Sub Tx one-off cost	48074.26	6009.28	48893.92	72429.25	Gamma	100.00	600.93
Fulvestrant: Sub Tx cost_Cytotoxic chemotherapy	60092.83	6009.28	48893.92	72429.25	Gamma	100.00	600.93
Fulvestrant: Sub Tx one-off cost	48074.26	6009.28	48893.92	72429.25	Gamma	100.00	600.93

Appendix H. Literature searches for the clinical assessment

Not applicable.

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

Table 92. Bibliographic databases included in the literature search

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

Table 93. Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
N/A	N/A	N/A	N/A

Table 94. Conference material included in the literature search

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

H.1.1 Search strategies

Table 95. Search strategy table for

No.	Query	Results
#1	N/A	N/A
#2	N/A	N/A

H.1.2 Systematic selection of studies

Table 96. Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	N/A	N/A	N/A

Intervention	N/A	N/A	N/A
Comparators	N/A	N/A	N/A
Outcomes	N/A	N/A	N/A
Study design/publication type	N/A	N/A	N/A
Language restrictions	N/A	N/A	N/A

Table 97. Overview of study design for studies included in the analyses

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	N/A	N/A	N/A	N/A	N/A	N/A

H.1.3 Excluded fulltext references

N/A

H.1.4 Quality assessment

N/A

H.1.5 Unpublished data

N/A

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

Not applicable.

I.1 Health-related quality-of life search

N/A

Table 98. Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
N/A	N/A	N/A	N/A

Table 99. Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A

Table 100. Conference material included in the literature search

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

I.1.1 Search strategies

N/A

Table 101. Search strategy for [name of database]

No.	Query	Results
#1	N/A	N/A

I.1.2 I.1.2 Quality assessment and generalizability of estimates

N/A

I.1.3 I.1.3 Unpublished data

N/A

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

Not applicable.

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

N/A

J.1.1 J.1.1 Example: Systematic search for [...]

N/A

Table 102. Sources included in the search

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

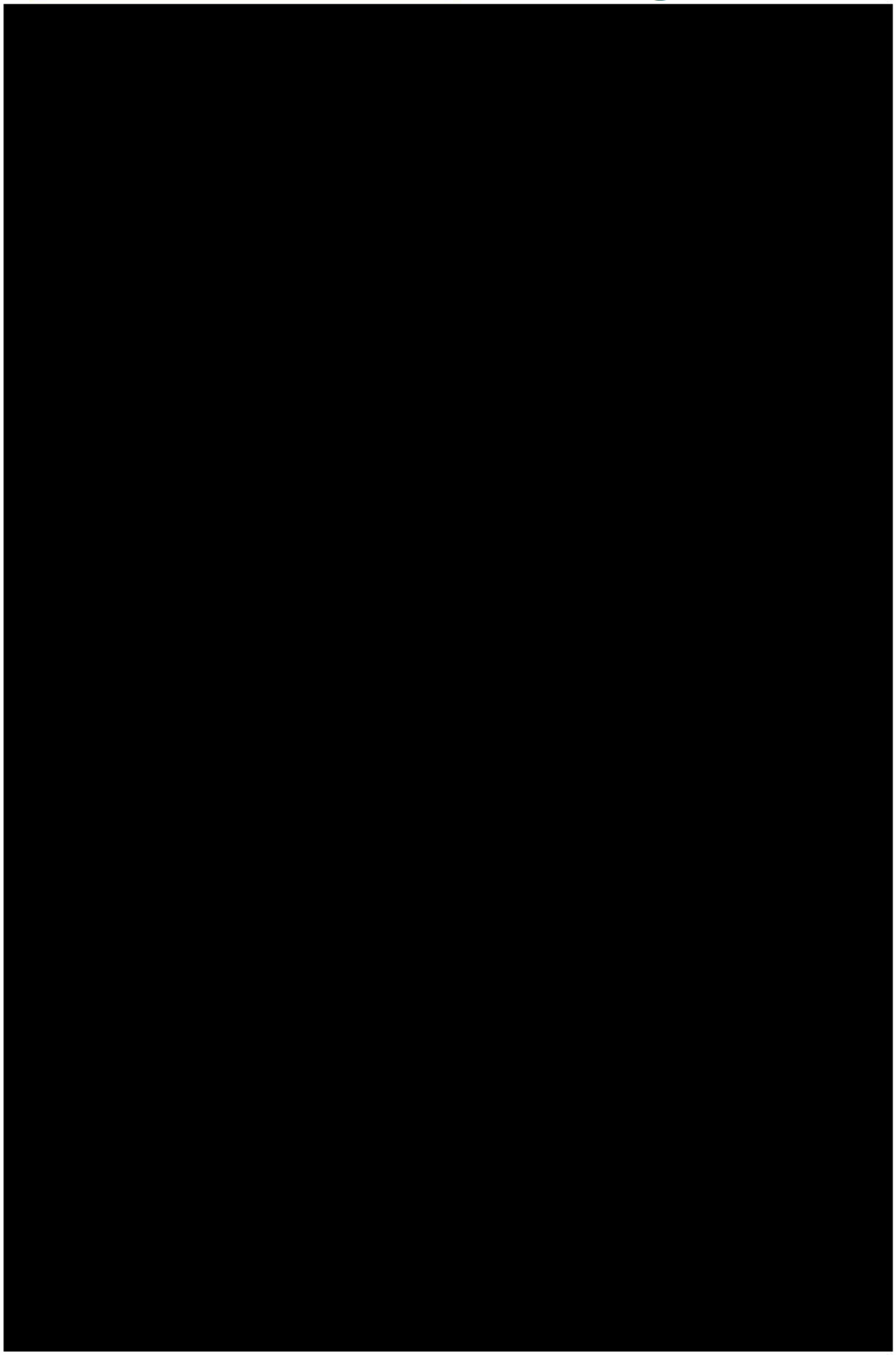
J.1.2 J.1.2 Example: Targeted literature search for [estimates]

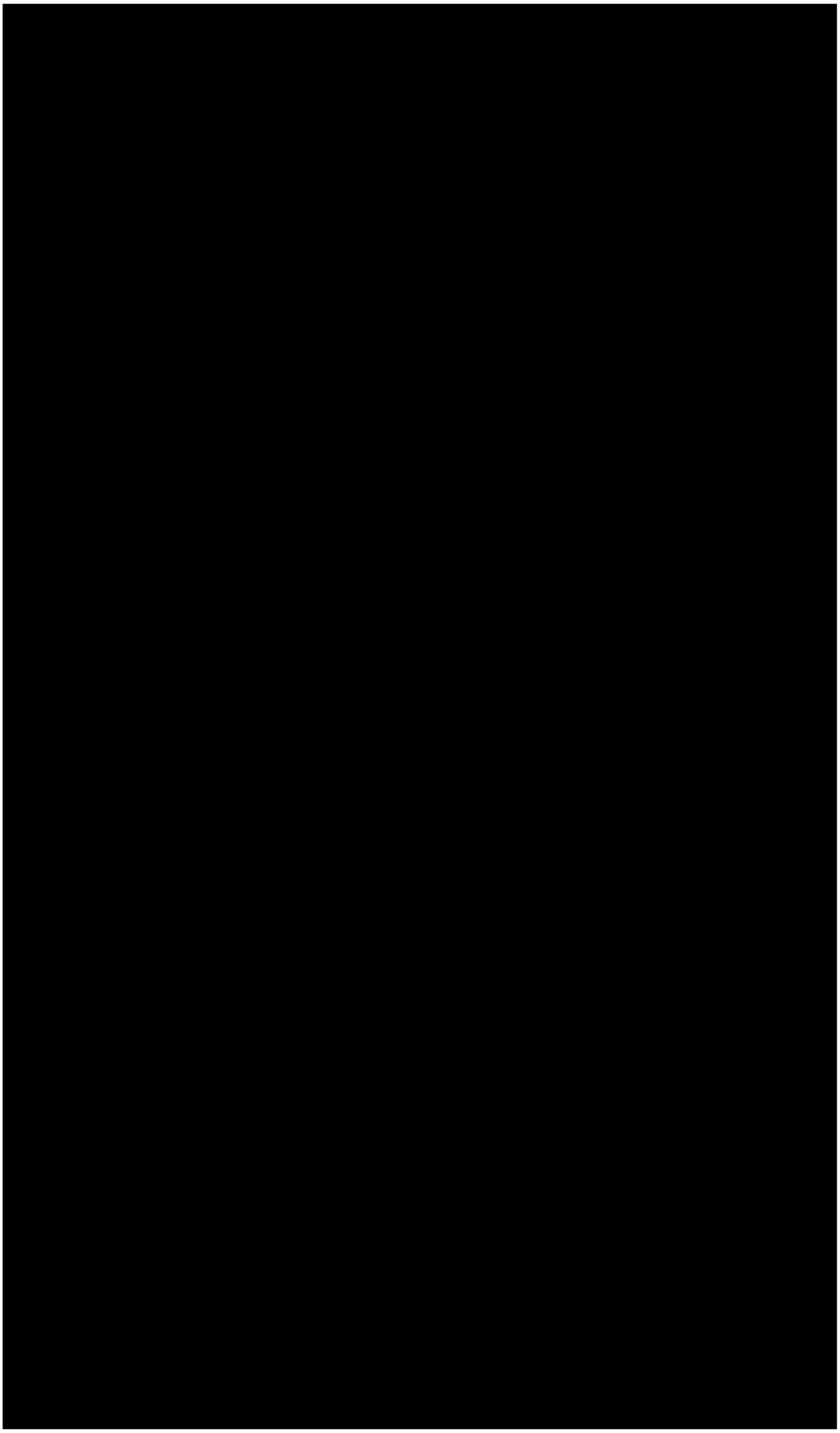
N/A

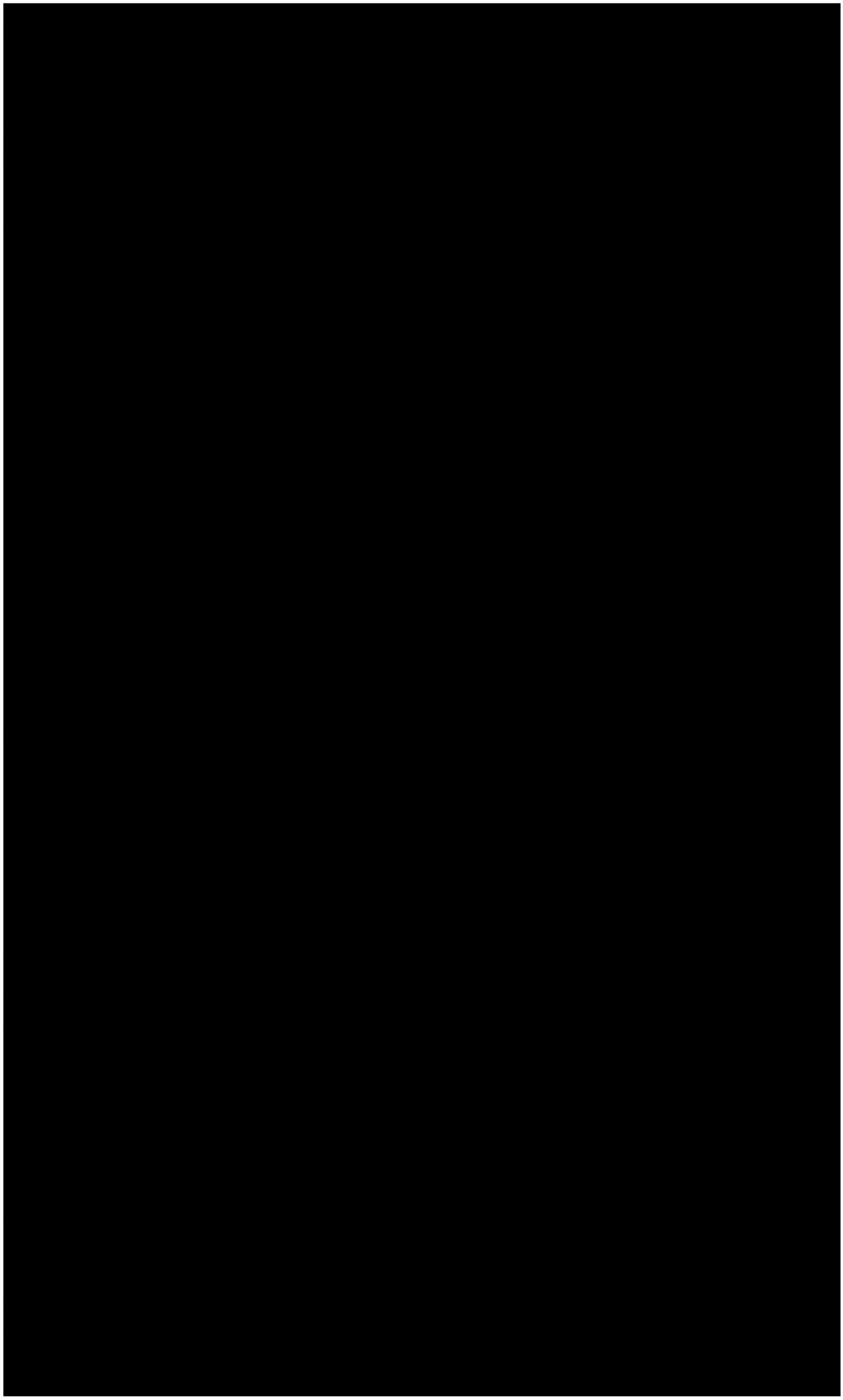
Table 103. Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
N/A	N/A	N/A	N/A

Appendix K. Real-world evidence – Study objectives and design







[redacted]

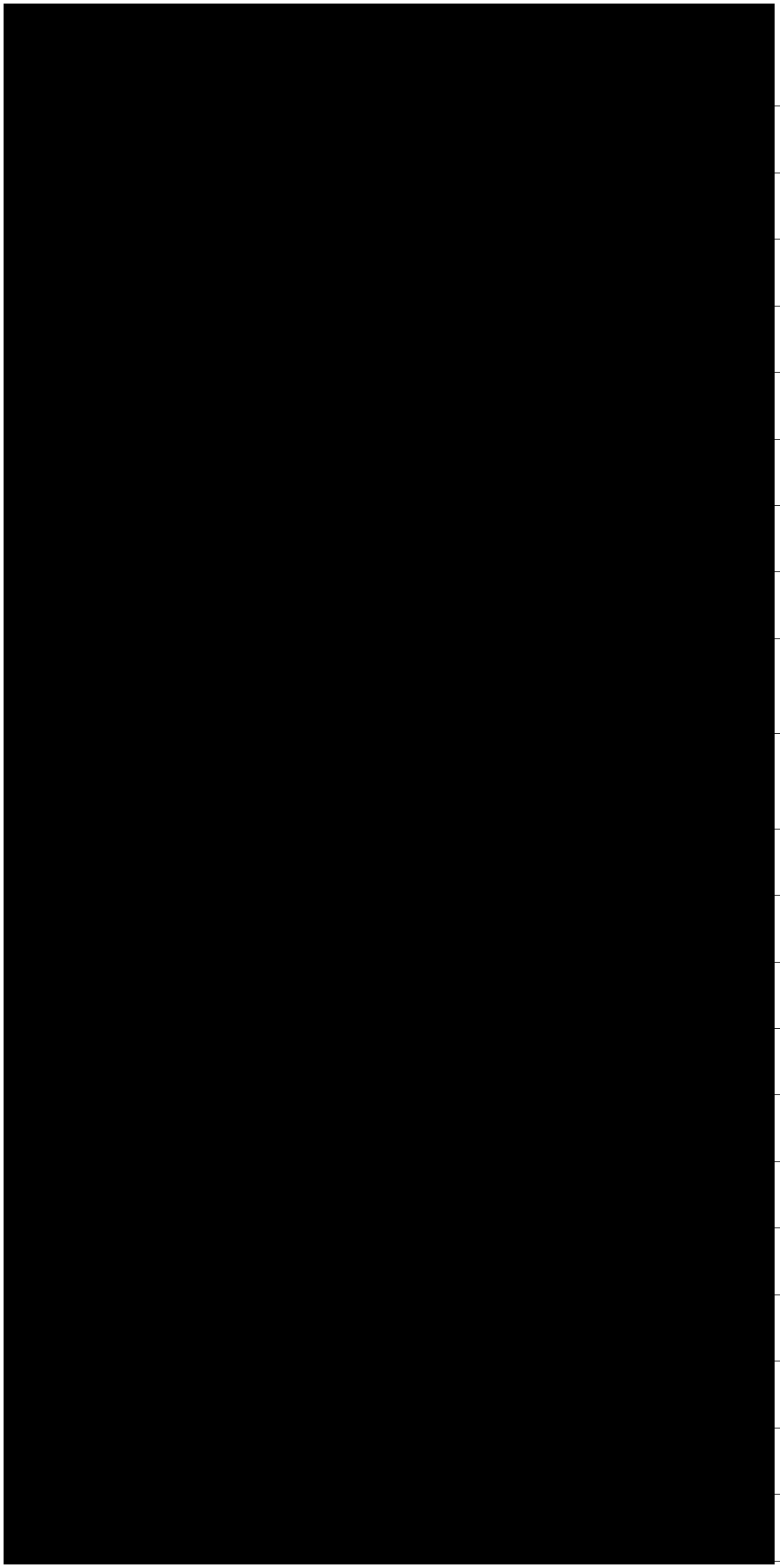
Appendix L. Summaries of most common AEs

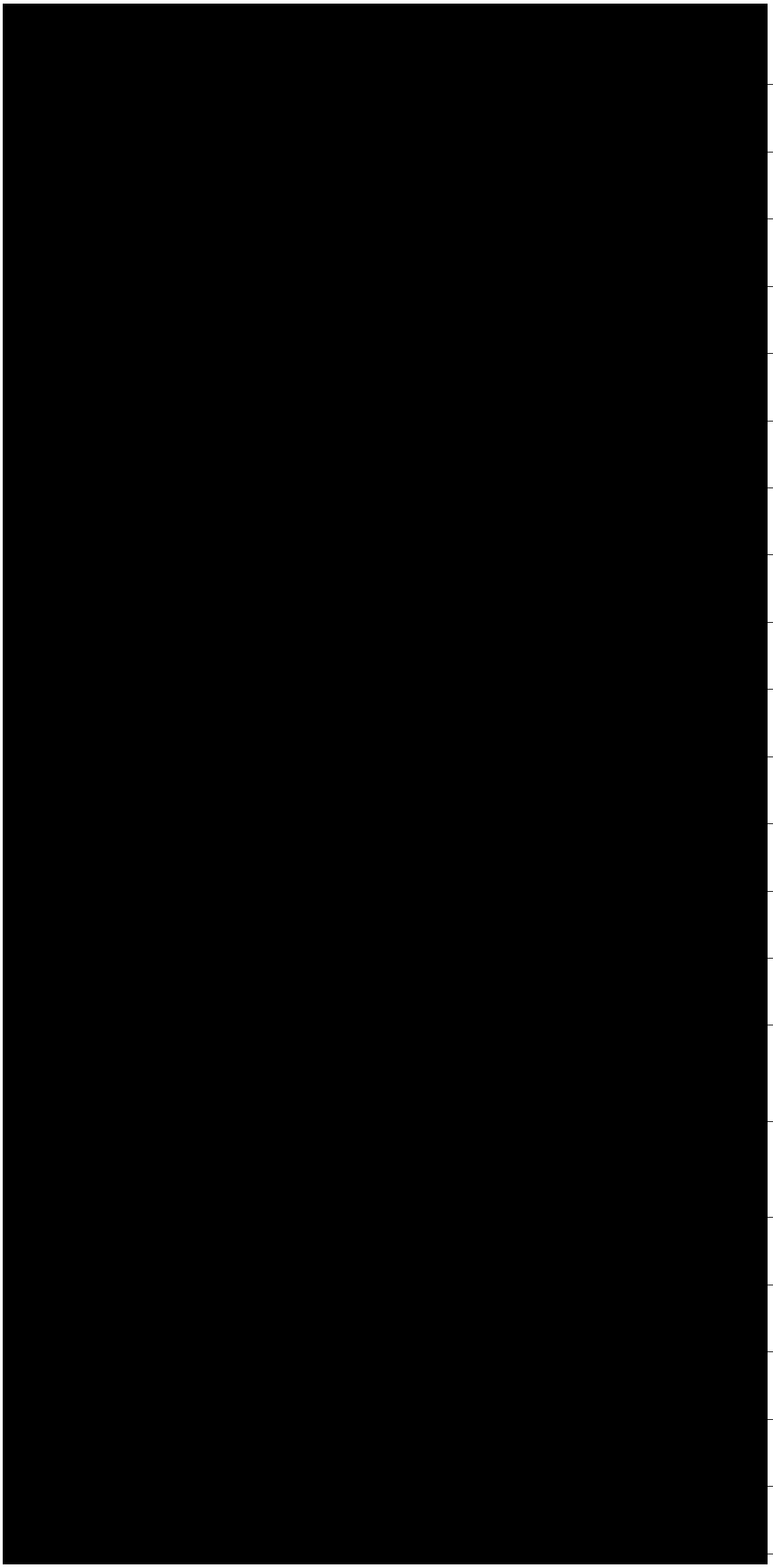
Summaries of most common AEs are provided in the table below (SAS).

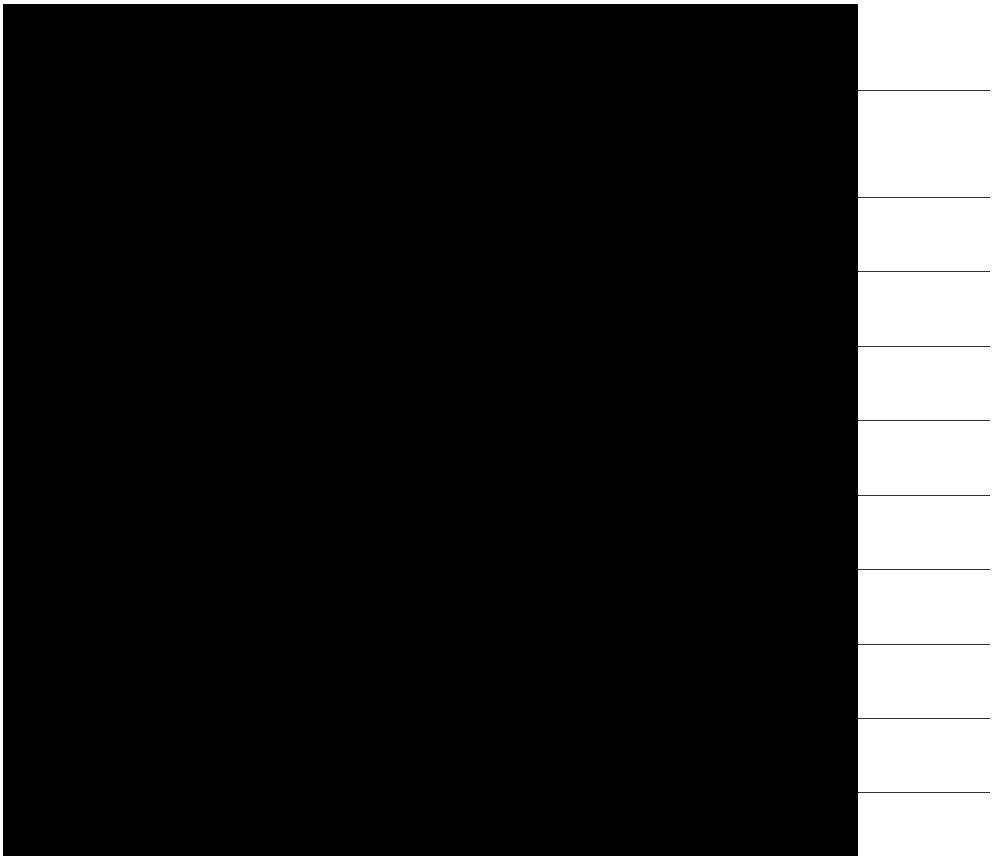
Table 106 Adverse events, most common (frequency of > 2% in either treatment arm), by preferred term (Safety analysis set, DCO2)

MedDRA Preferred Term	Capivasertib + Fulvestrant (N=355)	Placebo + Fulvestrant (N=350)

[redacted]







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