Medicinrådet

Bilag til Medicinrådets vurdering af pertuzumab i kombination med trastuzumab til adjuverende behandling af tidlig HER2-positiv brystkræft

Vers. 2.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. pertuzumab i kombination med trastuzumab
2. Forhandlingsnotat fra Amgros vedr. pertuzumab i kombination med trastuzumab
3. Ansøgers endelige ansøgning vedr. pertuzumab i kombination med trastuzumab

Høringssvar fra Roche Pharmaceuticals A/S vedrørende Medicinrådets anbefaling vedr. Perjeta (pertuzumab) til behandling af tidlig HER2-positiv brystkræft.

Roche takker for det fremsendte udkast til Medicinrådets vurderingsrapport af Perjeta (pertuzumab) til behandling af tidlig HER2-positiv brystkræft. Roche ønsker at kommentere på en række punkter i både den kliniske og den sundhedsøkonomiske vurdering.

- Roche ønsker at fremhæve, at der for den relevante patientpopulation, i den nuværende kliniske praksis eksisterer en behandlingsmæssig ulighed. Dette er gældende for en mindre gruppe af patienter, anslået til ca. 50 kvinder årligt, som ved den initiale udredning fejlagtigt diagnosticeres som enten lymfeknude negative (N0) eller HER2-negative, men som efterfølgende ved operation viser sig at være henholdsvis lymfeknude positive (N+) eller HER2-positive. Disse patienter har en risikoprofil, der er sammenlignelig med den patientgruppe, som i dag modtager neoadjuverende kemoterapi (NACT) i kombination med pertuzumab og trastuzumab. På trods heraf har den relevante patientpopulation i dag ikke adgang til dobbelt HER2-blokade, alene som følge af diagnostisk diskrepans mellem initial biopsi og endelig patologisk vurdering.

  En anbefaling af pertuzumab som adjuverende behandling vil sikre, at patienter, som på baggrund af en initial HER2-negativ biopsi eller vurderes som N0 under udredningen, men som efterfølgende viser sig at have HER2-positiv sygdom eller N+ ved operation, får adgang til målrettet behandling på lige fod med den gruppe patienter, som initialt diagnosticeres korrekt. Det bør ligeledes bemærkes, at omkostningen for sundhedsvæsenet til behandlingen af disse patienter i dag er lavere end for patienter der diagnosticeres korrekt præoperativt. De inkrementelle omkostninger og ICER fra Medicinrådets analyse bør ses med dette in mente.

- Medicinrådet påpeger, at det udgør en usikkerhed i datagrundlaget for klinisk effekt, at overlevelsesdata ikke er modne, og at median OS endnu ikke er opnået for hverken intervention eller komparator. Roche er ikke enige i denne vurdering og ønsker at understrege, at de foreliggende OS-data fra APHINITY-studiet må betragtes som modne. De data, der er præsenteret i ansøgningen, stammer fra den finale OS-analyse. I samråd med både EMA og FDA blev studiedesignet justeret fra et hændelsesdrevet til et tidsdrevet endepunkt, defineret som 10 år efter, at den sidste patient havde afsluttet målrettet behandling. Med en median opfølgning på 11,3 år vurderes datasættet derfor som tilstrækkeligt modent. Data viser desuden en statistisk signifikant forbedring i samlet overlevelse for patienter med N+ sygdom, med en hazard ratio på 0,79. Dette adresserer den usikkerhed, som lå til grund for Medicinrådets afslag i 2018, og bør tilsvarende reducere usikkerheden i den aktuelle vurdering.
  Roche finder det derudover metodisk uhensigtsmæssigt at tillægge manglende median OS væsentlig betydning i et adjuverende studie i kurativ setting. I sådanne studier, hvor den samlede overlevelse er høj, vil median OS typisk ikke kunne opnås inden for en klinisk relevant tidshorisont. I denne kontekst er hazard ratio et mere relevant og validt effektmål til vurdering af behandlingseffekt.

- Roche er enig med Medicinrådet i, at der ikke bør være klinisk usikkerhed forbundet med valget mellem intravenøs og subkutan administration af pertuzumab i kombination med trastuzumab. Evidensen fra FeDeriCa-studiet dokumenterer både farmakokinetisk ækvivalens og klinisk non-inferiority mellem de to administrationsformer.

- Roche anerkender Medicinrådets vurdering af, at tillæg af pertuzumab til trastuzumab medfører flere bivirkninger end trastuzumab alene. Samtidig understreges det, at sikkerhedsprofilen er velkendt, uden nye eller uventede hændelser, og vurderes som acceptabel og håndterbar i klinisk praksis, både af EMA og af fagudvalget i Medicinrådets tidligere vurdering fra 2018. EQ-5D-3L-data viser desuden, som beskrevet i vurderingsrapporten, at tillæg af pertuzumab ikke forringer patienternes helbredsrelaterede livskvalitet sammenlignet med trastuzumab og kemoterapi alene. Samlet viser dette, at bivirkningsbyrden er forventelig, håndterbar og ikke ledsaget af forringet livskvalitet hos patienterne.

- Roche undrer sig over hvorfor der i Medicinrådets beregning af lægemiddelomkostninger antages at patienter modtager en støddosis (1200+600 mg Phesgo eller 8 mg/kg trastuzumab) i cyklus 9. Dette var ikke behandlingspraksis i Aphinity og fremgår heller ikke af Medicinrådets oprindelige vurdering.

- Roche finder det ikke rimeligt eller retvisende at der i Medicinrådets hovedanalyse antages at være det samme niveau af omkostninger forbundet med administration af subkutan pertuzumab+trastuzumab versus intravenøs trastuzumab. Denne tilgang tilgodeser ikke værdien af, at anvendelsen af Phesgo medfører en besparelse på sundhedsvæsenets i forvejen begrænsede kapacitet. Roche mener derfor at følsomhedsanalysen, hvor *DRG-taksten tilskrives ved hver administration ekstra omkostning for timelønnen fra en sygeplejerske* bør tillægges større vægt end hovedanalysen og være udgangspunktet for beslutningsgrundlaget som Rådet tager stilling til.

[redacted]

Vi håber, at Medicinrådet vil tage disse overvejelser med i rådets endelige beslutning og dermed facilitere en mere retfærdig og lige adgang til pertuzumab i tidlig HER2-positiv brystkræft.

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31.03.2026

LSC/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	29.04.2026
Leverandør	Roche
Lægemiddel	Phesgo (pertuzumab + trastuzumab)
Ansøgt indikation	Pertuzumab i kombination med trastuzumab og kemoterapi som adjuverende behandling af voksne patienter med HER2-positiv tidlig brystkræft med høj risiko for tilbagefald.
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse (revurdering)

Prisinformation

Amgros har følgende aftalepris på Phesgo (pertuzumab + trastuzumab):

Tabel 1: Aftalepris

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Nuværende rabat ift. AIP
Phesgo	1.200+600 mg (1 stk.)	46.163,10	[redacted]	[redacted]
Phesgo	600+600 mg (1 stk.)	28.014,94	[redacted]	[redacted]

Aftaleforhold

Amgros har en eksisterende aftale på Phesgo. Aftalen løber indtil 31.03.2027 med mulighed for forlængelse i op til 24 måneder. Phesgo indgår i udbuddet på HER2-positiv brystkræft. Da der indgår biosimilære lægemidler i dette udbud, er det ikke muligt at prisregulere.

Informationer fra forhandlingen

Leverandøren har ikke mulighed for sænke prisen på Phesgo i forbindelse med denne vurdering, da Phesgo indgår i et udbud uden prisregulering grundet biosimilær konkurrence.

[redacted]

Konkurrencesituationen

Phesgo er en præblandet subkutan formulering af pertuzumab og trastuzumab. Medicinrådet har en behandlingsvejledning vedr. HER2-positiv brystkræft hvor Phesgo indgår. Et nyt udbud baseret på behandlingsvejledningen trådte i kraft den 01.04.2026.

[redacted] Biosimilær trastuzumab er markedsført i Danmark.

Den ansøgte indikation, adjuverende behandling af voksne patienter med HER2-positiv tidlig brystkræft med høj risiko for tilbagefald, inkluderer patienter der ikke initialt har påvist lymfeknudemetastaser eller HER2-positiv status, men hvor det efterfølgende påvises. Disse patienter tilbydes i dag trastuzumab.

Tabel 2 viser lægemiddeludgifter for hhv. Phesgo (pertuzumab + trastuzumab) og Ogivri (biosimilær trastuzumab), for et behandlingsforløb på 17 serier (hver af tre ugers varighed), jf. Medicinrådets vurdering af pertuzumab i kombination med trastuzumab til adjuverende behandling af tidlig HER2-positiv brystkræft. Administreres pertuzumab + trastuzumab som intravenøs infusion i stedet for præblandet subkutant Phesgo er lægemiddeludgiften for et behandlingsforløb på 17 uger [redacted]

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient for et behandlingsforløb på 17 serier

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandling (SAIP, DKK)
Phesgo	1.200+600 mg (1 stk.) 600+600 mg (1 stk.)	Serie 1: 1200+600 mg hver 3. uge, s.c. Serie 2-17: 600+600 mg hver 3. uge, s.c.	[redacted]	[redacted]
Ogivri	420 mg (1 stk.)	Serie 1: 8 mg/kg*, i.v. Serie 2-17: 6 mg/kg, i.v.	[redacted]	[redacted]

*Vægt 74,3 kg, jf. Medicinrådets vurdering af pertuzumab i kombination med trastuzumab til adjuverende behandling af tidlig HER2-positiv brystkræft

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Delvis anbefalet	Link til vurdering
England	Delvis anbefalet	Link til vurdering
Sverige	Anbefalet	Link til vurdering

Opsummering

[redacted]

[redacted]

Application for the assessment of pertuzumab in combination with trastuzumab for adjuvant treatment of HER2-positive early breast cancer at high risk of recurrence

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

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Abbreviations

A	Doxorubicin
AE	Adverse Event
AIC	Akaike Information Criteria
AUC	Area under curve
BC	Breast Cancer
BIC	Bayesian Information Criterion
C	Cyclophosphamide
CCOD	Clinical Cut-Off Date
CI	Confidence Interval
CTCAE	Common Terminology Criteria for Adverse events
D	Docetaxel
DBCG	Danish breast cancer group
DFS	Disease Free Survival
DMC	Danish Medicines Council
DRFI	Distant Recurrence-Free Interval
DRG	Diagnose Relative Group
DSA	Deterministic sensitivity analysis
E	Epirubicin
eBC	Early breast cancer
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EQ-5D-3L	European Quality of Life 5-Dimension 3-Level Questionnaire
EQ-5D-5L	European Quality of Life 5-Dimension 5-Level Questionnaire
ER	Estrogen receptor
ET	Endocrine therapy
EtM	Event to monitor
F	5-Fluorouracil
FISH	fluorescence in situ hybridization
HER2	Human epidermal growth factor receptor 2
HER2+	Human epidermal growth factor receptor 2-positive

HR+	Hormone receptor positive
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
HSUV	Health State Utility Values
HT	Herceptin+Chemotherapy
ICER	Incremental Cost-Effectiveness Ratio
IDFS	Invasive Disease-Free Survival
IHC	Immunohistochemistry
ISH	in situ hybridization
ITT	Intent-To-Treat
KM	Kaplan-Meier (curve)
LVEF	Left Ventricular Ejection Fraction
LVSD	Left ventricular systolic dysfunction
mBC	metastatic breast cancer
MUGA	Multiple-Gated Acquisition
N+	Node positive
NMB	Net monetary benefit
NYHA	New York Heart Association
OS	Overall Survival
pCR	Pathological complete response
PFS	Progression-Free Survival
PH	Proportional Hazard
PHT	Pertuzumab+Herceptin+Chemotherapy
Pla+H+Chemo	Placebo+Herceptin+Chemotherapy
PPS	Post-progression survival
PR	Progesterone Receptor
PRO	Patient-reported outcome
PSA	Probabilistic Sensitivity Analysis
PT	Preferred Term
Ptz+H+Chemo	Pertuzumab+Herceptin+Chemotherapy
Q3W	Every three weeks
QALY	Quality-Adjusted Life-Year
QLQ-BR23	QLQ-Breast Cancer Module 23
RFI	Recurrence-Free Interval
SAE	Serious Adverse Event
SD	Standard deviation
SE	Standard Error
SPNBC	Second primary non-breast cancers
STEEP	standardized definitions for efficacy end points
T	Paclitaxel
T-DM1	trastuzumab emtansine (Kadcyla)
T-DXd	trastuzumab deruxtecan (Enhertu)
TC	Carboplatin
TP	Transition propabilities
TRTb-Ch	trastuzumab biosimilar + chemotherapy
TTOT	Time-to-off treatment

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Perjeta
Generic name	Pertuzumab
Therapeutic indication as defined by EMA	Perjeta is indicated for use in combination with trastuzumab and chemotherapy in the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence
Marketing authorization holder in Denmark	Roche Registration GmbH, Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen, Germany
ATC code	L01FD02
Combination therapy and/or co-medication	Trastuzumab and chemotherapy (standard anthracycline- and/or taxane-based chemotherapy)
Date of EC approval	28-Jun-2018
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	Early breast cancer: Perjeta is indicated for use in combination with trastuzumab and chemotherapy in the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early-stage breast cancer at high risk of recurrence. Metastatic breast cancer: Perjeta is indicated for use in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.
Other indications that have been evaluated by the DMC (yes/no)	Yes. Pertuzumab (Perjeta®) in combination with trastuzumab (Herceptin®) for adjuvant treatment of early HER2+ breast cancer. Assessed in 2018, not recommended.
Joint Nordic assessment (JNHB)	Treatment practices are similar across the Nordic countries; however, the product is not suitable for Joint Nordic Assessment as this is an old indication, which was reimbursed by other countries many years ago.

Overview of the medicine	
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Pertuzumab 420 mg concentrate for solution for infusion. One 14 ml vial of concentrate contains 420 mg of pertuzumab at a concentration of 30 mg/ml.

2. Summary table

Summary	
Indication relevant for the assessment	Perjeta is indicated for use in combination with trastuzumab and chemotherapy in the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence.
Dosage regiment and administration	The dosage regimen consisted of trastuzumab and pertuzumab (or placebo)—administered for a total of 52 weeks, concurrent with chemotherapy. Trastuzumab was given as an IV infusion with a loading dose of 8 mg/kg, followed by maintenance dose of 6 mg/kg every three weeks. Pertuzumab (or placebo) was given as an IV infusion with a loading dose of 840 mg, followed by maintenance doses of 420 mg every three weeks.
Choice of comparator	Trastuzumab and chemotherapy
Prognosis with current treatment (comparator)	For patients with HER2-positive early breast cancer and nodal involvement treated with the current standard adjuvant therapy (trastuzumab plus chemotherapy), the disease remains progressive for a substantial proportion of patients. Despite effective treatment, approximately 25% experience disease recurrence within 8–10 years (1). Metastatic breast cancer (mBC) remains an incurable disease, where treatment is primarily aimed at prolonging survival and maintaining quality of life. This stage is often associated with a marked reduction in life expectancy and health-related quality of life (HRQoL). Danish real-world evidence indicates a median overall survival of 37.1 months for patients with recurrent HER2-positive metastatic breast cancer (2). The presence or absence of axillary lymph node involvement is the most powerful independent prognostic factor in early breast cancer treated with adjuvant or neoadjuvant/adjuvant systemic therapy (3). Even in the setting of trastuzumab-based

Summary	
	adjuvant treatment, lymph node–positive disease confers a significantly higher risk of recurrence and mortality compared with node-negative disease (4-6). Thus, this subgroup represents high-risk early breast cancer, treated with curative intent, but with a substantial residual risk of relapse despite optimal current standard therapy.
Type of evidence for the clinical evaluation	APHINITY is a head-to-head study and provides a direct comparison of pertuzumab in combination with trastuzumab and chemotherapy and trastuzumab and chemotherapy for treatment of HER2-positive patients in adjuvant setting.
Most important efficacy endpoints (Difference/gain compared to comparator)	Efficacy endpoint for the N+ subgroup constituted around 63% of the ITT study population. **<u>Primary endpoint</u>** **Invasive disease-free survival (IDFS) excluding second primary non-breast cancers (SPNBC)** **Primary analysis - Median follow-up ≈ 45 months.** *Pertuzumab:* 92.0% (90.59, 93.40) *Placebo:* 90.2% (88.63, 91.69) *Hazard* Ratio (HR): 0.77 (95% CI, 0.62–0.96; P = 0.02) **Final analysis - Median follow-up 11.25 years.** *Pertuzumab:* 84.58% (82.68, 86.49) *Placebo:* 79.55% (77.43, 81.67) *Hazard Ratio (HR):* 0.74 (95% CI. 0.62, 0.88; 0.0006) **<u>Secondary endpoint</u>** ***Overall survival (OS)*** **Primary analysis - Median follow-up ≈ 45 months.** Data were immature at primary analysis. **Final analysis - Median follow-up 11.25 years.** *Pertuzumab: 89.55% (97.93, 91.17)* *Placebo: 86.87% (85.08, 88.66)* *Hazard Ratio (HR):* 0.79 (95% CI. 0.64, 0.97; 0.0261)
Most important serious adverse events for the intervention and comparator	**Febrile neutropenia** Febrile neutropenia was the only SAE with a frequency ≥5%. *Pertuzumab*: 8.8% (208 patients) *Placebo*: 8.1% (196 patients) No SAEs had a frequency of ≥ 5% in the post-treatment period. **Diarrhea (Grade 3–4)** Most frequent during targeted therapy + taxane chemotherapy: *Pertuzumab:* 8.4% *Placebo:* 2.5%

Summary	
	Incidence decreased during post-chemotherapy targeted therapy: *Pertuzumab*: 0.5% *Placebo:* 0.2% **Rash (Grade 3–4)** *Pertuzumab*: 2.5% (59 patients) *Placebo:* 1.5% (36 patients)
Impact on health-related quality of life	Based on EQ-5D-3L mapped to EQ-5D-5L no statistically significant difference in health-related quality of life was shown. At base the difference is [redacted], at end of treatment the difference is [redacted] and at 36 months of follow up the difference is [redacted]. In the health economic model, the utility is equal to the comparator
Type of economic analysis that is submitted	Cost-utility Semi-Markov model for IDFS survival related part (time-dependent transition probabilities) is based on individual patient data from the APHINITY trial. After IDFS model assumes constant transition probabilities (traditional state transition Markov model)
Data sources used to model the clinical effects	APHINITY trial for IDFS Risk of disease progression in 1st line metastatic setting (early disease recurrence) is derived from the PFS data of the EMILIA trial. Risk of disease progression in 1st line metastatic setting (metastatic recurrence 18 months) is estimated from CLEOPATRA (PHT and HT) and M77001 trials (chemotherapy) Risk of death upon metastatic progression is estimated from CLEOPATRA (PHT and HT) and M77001 trials (chemotherapy)
Data sources used to model the health-related quality of life	Early breast cancer: APHINITY trial (crosswalk from EQ-5D-3L to EQ-5D-5L using and with the Danish tariff) Recurrence / metastatic: From the literature based on Lloyd et al (7)
Life years gained	0,511
QALYs gained	0,470
Incremental costs	[redacted]

Summary	
ICER (DKK/QALY)	[redacted]
Uncertainty associated with the ICER estimate	The results were robust with respect to decision uncertainty, while the model time horizon and discount rates were identified as the most influential factor from the parametric uncertainty perspective.
Number of eligible patients in Denmark	Incidence: 62 Prevalence: Not available
Budget impact (in year 5)	[redacted]

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

3.1 The medical condition

In 2023, 5,412 Danish women were diagnosed with breast cancer (BC), making it the most common cancer among women (8). BC is also the leading cause of cancer-related death in women, accounting for 14.4% of all female cancer deaths, equivalent to approximately 1,100 deaths annually in Denmark (9-11).

BC is defined as a malignant growth of epithelial cells in breast tissue and represents a heterogeneous disease with distinct biological subtypes, each with different clinical behavior and outcomes. Based on molecular classification, four main subtypes are recognized, hormone receptor-positive (estrogen receptor (ER) and/or progesterone receptor (PR) positive), HER2-positive (HER2 overexpression/amplification), triple-negative (ER, PR, and HER2 negative) and less common variants (e.g., HER2-enriched, luminal B) (12).

HER2-positive (HER2+) BC accounts for approximately 10–15% of all BC cases, corresponding to around 760 patients annually in Denmark. Of these, around 600 patients are typically treated with HER2-targeted therapies with curative intent (13).

BC arises from a multistep process of genetic and epigenetic changes that lead to uncontrolled proliferation and loss of normal growth regulation. HER2+ disease is characterized by overexpression of the HER2 receptor protein and/or amplification of

the HER2 gene, confirmed by validated immunohistochemistry (IHC) and/or in situ hybridization (ISH) (14, 15).

HER2 overexpression results in a more aggressive tumour biology, higher recurrence rates, and historically poor prognosis. Importantly, HER2 status also serves as a predictive biomarker, as tumors with HER2 amplification derive substantial benefit from HER2-targeted therapies (14).

BC, particularly in early stages, is often asymptomatic and typically detected by screening mammography or routine clinical examination (16). The most common presenting symptom is a painless breast lump, either self-detected or discovered during screening (17).

Overall, the 5-year survival rate for breast cancer in Denmark is around 90%, but survival varies substantially by subtype and stage at diagnosis (8, 9). Patients with HER2+ disease historically had poor outcomes, but prognosis has improved markedly with the introduction of trastuzumab and pertuzumab, both of which target the HER2 receptor (18, 19).

3.2 Patient population

Despite advances in therapy, approximately 25% of women with HER2+ early breast cancer (eBC) treated with trastuzumab-based adjuvant therapy still experience recurrence within 8–10 years (1, 4).

Metastatic breast cancer (mBC) remains an incurable disease, where treatment is primarily aimed at prolonging survival and maintaining quality of life rather than achieving cure. Findings from a Danish real-world study published in 2023 demonstrated that for patients with recurrent mBC, the median overall survival was only 37.1 months (2). This underscores the critical need to intensify adjuvant therapy for patients at high risk of recurrence with axillary lymph node involvement (N+), reducing relapse risk at the earliest stage when cure is still possible.

This application concerns therefore patients with early-stage, HER2+, N+ BC in Denmark who are at high risk of recurrence and have not received neo. adjuvant chemotherapy in combination with pertuzumab and trastuzumab.

Axillary lymph node status remains the most important prognostic factor in eBC and is associated with poorer outcomes even in patients treated with adjuvant chemotherapy and trastuzumab (3-6). In HER2+ eBC, axillary node involvement is consistently recognized as a high-risk feature that requires treatment escalation. Both the Danish Breast Cancer Group (DBCG) guidelines and international standards such as ESMO and St. Gallen classify patients with axillary node involvement as being at high risk of recurrence (20-22).

The clinical relevance of this subgroup is further reinforced by the APHINITY trial where nodal status was included as a randomization stratification factor and pre-specified subgroup analyses confirmed the prognostic importance of N+ disease (23, 24).

According to Danish data, approximately 44% of HER2+ eBC patients present with N+ disease and belong to this high-risk group (25).

Data from the DBCG database covering the years 2020 to 2024, (data requested by Roche (26)), show that 710 patients were diagnosed with HER2+ BC and macrometastases, defined as N+ disease. In that time period 375 patients received neoadjuvant chemotherapy in combination with pertuzumab and trastuzumab. In the same time period 335 patients out of the 710 patients were not offered neoadjuvant chemotherapy in combination with pertuzumab and trastuzumab, as recommended by both national and international guidelines (21, 22). Among the 335 patients approximately 9% were allocated outside protocol primarily due to a history of previous malignant disease for which reporting of systemic therapy is neither required nor feasible. In addition, around 15% had a documented omission of dual HER2 blockade. This leaves 259 patients who according to current treatment standards should have been offered neoadjuvant chemotherapy with dual HER2 blockade or adjuvant dual HER2 blockade. On average this corresponds to about 52 patients per year over the five-year period, and have not received neo. adjuvant chemotherapy in combination with pertuzumab and trastuzumab representing a misclassified and undertreated group of Danish patients.

Table 1 Incidence and prevalence in the past 5 years (27-31)

Year	2020	20221	2022	2023	2024
Incidence in Denmark	632	656	671	704	107
Prevalence in Denmark	9.610	9.828	10.042	10.281	10.525
Global prevalence	N/A	N/A	N/A	N/A	N/A

The incidence and prevalence estimates are derived from annual cancer statistics published by the Danish Health and Medicines Authority (27-31) . To estimate the number of patients with HER2+ BC in Denmark, the total number of BC cases is multiplied by the subtype distribution reported in SEER data, where HER2+ accounts for approximately 13 % of all cases (32).

Table 2 presents the estimated annual number of patients with N+ HER2+ eBC who currently are not treated according to Danish clinical guidelines recommending neoadjuvant chemotherapy combined with pertuzumab and trastuzumab or adjuvant chemotherapy combined with pertuzumab and trastuzumab based on DBCG registry data from 2020–2024 (26) .

Table 2 Estimated number of patients eligible for treatment (26)

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	52	54	56	58	60

3.3 Current treatment options

The current treatment pathway for patients with HER2+ eBC with N+ disease follows the current guidelines developed by DBCG (20).

The standard Danish treatment algorithm for patients with HER2+ eBC with N+ disease consist of neoadjuvant treatment with four cycles of anthracycline/ cyclophosphamide followed by four taxane-based chemotherapy in combination with trastuzumab and pertuzumab (20). The patients with HER2+ eBC, N+ disease and pathological complete response (pCR) are after neoadjuvant treatment offered to complete a full year of trastuzumab monotherapy in the adjuvant setting, see Figure 1 (20). This is in contrast with international guidelines which recommend patients with HER2+ eBC at high-risk of recurrence to complete a full year of dual HER2 blockade with pertuzumab plus trastuzumab in the adjuvant setting (20-22).

Figure 1 Current treatment algorithm for patients with HER2+, eBC with N+ disease and high risk of recurrence (20).

eBC, early breast cancer; ET, endocrine therapy; HER2+, Human epidermal growth factor receptor 2-positive; HR+, hormone receptor positive, N+, node positive.

Neoadjuvant chemotherapy in combination with pertuzumab and trastuzumab were introduced in Danish treatment guidelines in 2016, recommended for patients with HER2+ BC and with N+ and/or tumours > 2 cm, or locally advanced disease (20). Despite this numbers from the DBCG quality rapport shows that around 35% of patients eligible for neoadjuvant chemotherapy, did not receive the recommended neoadjuvant treatment in 2024 (11).

Patients who are not diagnosed with N+ disease prior to surgery but are found to have axillary lymph node involvement intraoperatively are currently not offered neoadjuvant chemotherapy in combination with pertuzumab and trastuzumab.
Instead, this patient group receives adjuvant treatment consisting of four cycles of anthracycline-based chemotherapy, followed by three cycles of taxane-based chemotherapy and one year of trastuzumab (see Figure 2) (20).

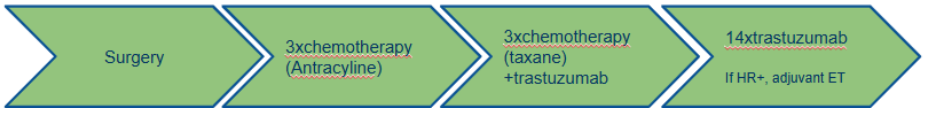

Figure 2 Current treatment algorithm for patients not initially diagnosed with N+ disease pre-surgery (20).

ET, endocrine therapy; HR+, Hormone receptor positive, N+, node positive.

Adjuvant pertuzumab is not available for Danish patients today, as DMC rejected its use back in 2018 (20, 33). Despite this Danish clinical guidelines in line with international guidelines recommend one year of trastuzumab plus pertuzumab and chemotherapy, for the group of patients with N+ disease and pCR who have not received neoadjuvant

chemotherapy in combination with pertuzumab and trastuzumab adjuvant pertuzumab (20). As this group of patients according to DBCG, belong to a group of misclassified patients who currently have no opportunity to receive pertuzumab in combination with trastuzumab and chemotherapy, either in the neoadjuvant or adjuvant setting.

Although advances in treatment with trastuzumab and chemotherapy in HER2+ eBC, the treatment outcomes for patients with N+ disease are still inferior compared to patients without nodal involvement. Data from APHINITY and HERA trials have consistently demonstrated that N+ patients have worse treatment outcome compared to patients without nodal involvement when treated with chemotherapy plus trastuzumab in the adjuvant setting (4, 19).

3.4 The intervention

Table 3 Overview of intervention (34)

Overview of intervention	
Indication relevant for the assessment	Perjeta is indicated for use in combination with trastuzumab and chemotherapy in the adjuvant treatment of adult patients with HER2+ eBC at high risk of recurrence.
ATMP	N/A
Method of administration	Pertuzumab was administered as IV infusion in the APHINITY study. In Danish clinical practice pertuzumab and trastuzumab are administered as Phesgo – a subcutaneous fixed-dose combination of pertuzumab and trastuzumab, offering a more time-efficient alternative to the IV administration of the two monoclonal antibodies given separately.
Dosing	Loading dose: 840 mg pertuzumab, followed every 3 weeks thereafter by a maintenance dose of 420 mg pertuzumab.
Dosing in the health economic model (including relative dose intensity)	In the health economic model the subcutaneous fixed-dose combination of pertuzumab and trastuzumab is used. Loading dose is 1.200 mg pertuzumab / 600 mg trastuzumab., followed by 600 mg pertuzumab / 600 mg trastuzumab as maintenance treatment every 3 weeks.
Should the medicine be administered with other medicines?	Pertuzumab should be administered in combination with trastuzumab and chemotherapy.
Treatment duration / criteria for end of treatment	Pertuzumab should be administered in combination with trastuzumab every 3 weeks for a total of 1 year (up to 18 cycles) or until disease recurrence, or unmanageable toxicity, whichever occurs first, as part of a complete regimen for eBC, including standard anthracycline and/or taxane-based chemotherapy (34).

Overview of intervention	
Necessary monitoring, both during administration and during the treatment period	Left Ventricular Ejection Fraction (LVEF).
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	HER2 status can be determined using two complementary methods, immunohistochemistry (IHC) or in situ Hybridization (ISH). Both are currently standard procedure in Danish clinical practice (15). Diagnostic tests were not included in the model.
Package size(s)	Pertuzumab comes with trastuzumab (and hyaluronidase) as a fixed-dose combination for S.C use. For loading dose 1,200 mg pertuzumab / 600 mg trastuzumab, 15 mL solution for injection in a 20 mL glass vial (1 vial per pack). For maintenance dose 600 mg pertuzumab / 600 mg trastuzumab, 10 mL solution for injection in a 15 mL glass vial (1 vial per pack).

3.4.1 Description of ATMP

N/A

3.4.2 The intervention in relation to Danish clinical practice

The implementation of the APHINTY regimen into Danish clinical practice will make pertuzumab an additional treatment option for the group of patients with the highest risk of recurrence in the adjuvant setting. The pertuzumab-trastuzumab combination plus chemotherapy was approved in the EU on 1 June 2018 for the adjuvant treatment of HER2+ eBC patients at high risk of recurrence (34).

The implementation of the APHINTY regimen will change the treatment algorithm for the group of patients described in section 3.3, which according to DBCG is a group of misclassified patients who currently have no opportunity to receive pertuzumab and trastuzumab in combination with chemotherapy, neither in the neo-adjuvant nor adjuvant setting.

See Figure 3 for the change in the treatment algorithm compared to the current Danish treatment algorithm, see Figure 2 for the current treatment algorithm.

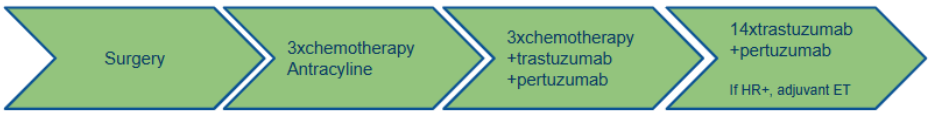

Figure 3 Change in the treatment algorithm compared to the current Danish treatment algorithm
ET, endocrine therapy; HR+, Hormone receptor positive

3.5 Choice of comparator(s)

In the APHINITY study, the comparator arm represented standard adjuvant therapy with chemotherapy plus trastuzumab and placebo. Chemotherapy was given according to the investigator's choice of an anthracycline-based or non-anthracycline regimen.

Table 4 Overview of comparator - trastuzumab (35)

Overview of comparator	
Generic name	Trastuzumab
ATC code	L01FD01
Mechanism of action	Trastuzumab are a recombinant humanised IgG1 monoclonal antibody which targets the human epidermal growth factor receptor 2 (HER2). Trastuzumab binds to sub-domain IV, of the extracellular domain of the HER2 protein to inhibit the ligand-independent, HER2 mediated proliferation and survival signals in human tumor cells that over express HER2.
Method of administration	Trastuzumab was administered as IV infusion in the APHINITY study.
Dosing	Trastuzumab was administered on Day 1 of Cycle 1 as an intravenous loading dose of 8 mg/kg. Beginning three weeks after the initial administration, and every three weeks (q3w) thereafter, patients received trastuzumab at a maintenance dose of 6 mg/kg for subsequent cycles.
Dosing in the health economic model (including relative dose intensity)	Planned dosing with vial sharing; 100%.
Should the medicine be administered with other medicines?	Trastuzumab was administered in combination with chemotherapy, either in an anthracycline containing regimen (6-8 cycles) or a non-anthracycline containing regimen (6 cycles).
Treatment duration/ criteria for end of treatment	A patient completed study treatment upon receiving the maximum of 18 cycles of targeted therapy over 52 weeks (+ 3-day window).
Need for diagnostics or other tests (i.e. companion diagnostics)	HER2 status was in the APHINITY study determined using one of two complementary methods, (IHC or FISH/chromogenic in situ hybridization.
Package size(s)	15 ml vial containing 150 mg powder for concentrate for solution for infusion.

Table 5 Overview of comparator - chemotherapy of combination regimens (36-42)

Overview of comparator	
Generic name	Approved chemotherapy consisted of combination regimens chosen by the investigator. Components included: 5-Fluorouracil (F), Epirubicin (E), Doxorubicin (A), Cyclophosphamide (C), Docetaxel (D), Paclitaxel (T), and Carboplatin (TC)
ATC code	L01BC02 (F), L01DB03 (E), L01DB01 (A), L01AA01 (C), L01CD02 (D), L01CD01 (T), L01XA02 (TC)
Mechanism of action	Cytotoxic agents interfering with DNA synthesis, replication, and mitosis, leading to cell-cycle arrest and apoptosis.
Method of administration	All approved chemotherapies were administered as IV infusion in the APHINITY study.

Dosing	Determined according to the Investigator's choice of chemotherapy regimen, which could be either anthracycline-based (FEC/FAC or AC/EC followed by a taxane) or non-anthracycline-based (TCH).
	Anthracycline-based regimens:
	Patients received either FEC, FAC, or AC/EC, followed by docetaxel or paclitaxel.
	• Anthracycline components (F, E, A, C) were typically administered every 3 weeks for 3 or 4 cycles.
	• Example dose ranges per m^2:
	  ○ 5-Fluorouracil: 500–600 mg/m^2
	  ○ Epirubicin: 90–120 mg/m^2
	  ○ Doxorubicin: 50 mg/m^2 (in FAC) or 60 mg/m^2 (in AC)
	  ○ Cyclophosphamide: 500–600 mg/m^2
	• Taxane components:
	  ○ Docetaxel: 75–100 mg/m^2 every 3 weeks for 3 or 4 cycles. Where docetaxel 75 mg/m^2 was used and not escalated to 100 mg/m^2, a total of 4 cycles was required.
	  ○ Paclitaxel: 80 mg/m^2 administered once weekly for 12 consecutive weeks.
	• Maximum cumulative doses permitted 360 mg/m^2 for doxorubicin and 720 mg/m^2 for epirubicin.
	
	Non-anthracycline regimen:
	Docetaxel 75 mg/m^2 plus carboplatin AUC 6 (maximum dose 900 mg), every 3 weeks for 6 cycles.

Dosing in the health economic model (including relative dose intensity)	Planned dosing with vial sharing; 100%.

Overview of comparator	
Should the medicine be administered with other medicines?	In combination with pertuzumab and trastuzumab.
Treatment duration/ criteria for end of treatment	Criteria for the end of the full study treatment included completing the required cycles or until disease recurrence, or unmanageable toxicity, whichever occurs first.
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A
Package size(s)	5-Fluorouracil: 50 mg/ml, Package size: 10 ml, 50 ml, 100 ml Epirubicin: 2 mg/ml, Package size: 25 ml, 50 ml, 100 ml Doxorubicin: 2 mg/ml, Package size: 5 ml, 25 ml, 100 ml Cyclophosphamide: Powder for solution, Package size:200 mg, 500 mg, 1 g, 2 g vials Docetaxel: 20 mg/ml, Package size: 1 ml (20 mg), 4 ml (80 mg), 8 ml (160 mg) Paclitaxel: 6 mg/ml, Package size: 16.7 ml, 25 ml, 50 ml Carboplatin: 10 mg/ml, Package size: 15 ml, 45 ml, 60 ml

3.6 Cost-effectiveness of the comparator(s)

In the APHINITY study, the combination of pertuzumab, trastuzumab, and chemotherapy was compared with trastuzumab and chemotherapy. In this economic evaluation pertuzumab and trastuzumab are used with combination product Phesgo. As trastuzumab in combination with chemotherapy is considered standard of care in clinical practice in Denmark and recommended by the DMC, it is reasonable to assume its cost-effective. Therefore, no additional cost-effectiveness analysis for the comparator arm is provided.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Table 6 Efficacy outcome measures relevant for the application (23, 43)

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Primary Endpoint			

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Invasive Disease-Free Survival (IDFS) APHINITY	Median follow-up 11.3 years (135.3 months)	IDFS, defined as time from randomization to ipsilateral invasive BC recurrence, contralateral invasive BC, distant recurrence, or death due to any cause. Of note, this definition does not include SPNBCs as events.	Response was assessed by the investigator on the basis of physical examinations, CT scans, and other imaging modalities as clinically indicated
Secondary Endpoints			
Invasive Disease-Free Survival-Second Primary Non-Breast Cancer (IDFS-SPNBC) APHINITY	Median follow-up 11.3 years (135.3 months)	IDFS-SPNBC, defined in the same way as IDFS but including SPNBC as an event (with the exception of non-melanoma skin cancers and in situ carcinoma of any site).	See collection of primary outcome measure
Overall Survival (OS) APHINITY	Median follow-up 11.3 years (135.3 months)	OS, defined as the time from randomization to death attributable to any cause. Patients who were alive (including lost to follow-up) at the time of the analysis were censored at the last known alive date.	See collection of primary outcome measure

* Time point for data collection used in analysis (follow up time for time-to-event measures)
BC, breast cancer; Interval; IDFS, Invasive Disease-Free Survival; OS, overall survival; SPNBC, Second primary non-breast cancers.

Validity of outcomes

The primary and secondary endpoints in the APHINITY study are well-defined and golden standard endpoint within oncologic research (44). IDFS and OS have been used in prior DMC submissions for eBC and treatment guideline protocol (13, 45). Therefore, the clinical efficacy data derived from the APHINITY study is considered as relevant for Danish clinical practice.

4. Health economic analysis

4.1 Model structure

This submission requires decision-analytic modeling, which is applied in accordance with the DMC economic evaluation guidelines. A probabilistic semi-Markov state transition model using a monthly cycle length was constructed in Microsoft Excel® to explore the

health outcomes and costs associated with the adjuvant treatment of patients with HER2-positive early BC.

The model structure (Figure 4) is an updated version of the one used in the 2016 NICE (46) submission for Perjeta® in the neoadjuvant treatment of early HER2-positive breast cancer. It closely resembles structures published by Attard et al. (47) and was tested during a UK advisory board. Comments on the model can be found on health technology assessment websites, including NICE, where it was deemed clinically plausible and reflective of disease progression. State transitions in the model (regarding states 1, 2, 4, and 6 in Figure 4) are informed by efficacy data from the most recent data cut (clinical cut-off date (CCOD) 28 November 2024) of the APHINITY clinical study, with a median follow-up time of 11.3 years. External trial data are used for other state transitions. This section describes the general principles of the model and the health-state transitions. Transition probabilities and related data are discussed in more detail in Section 8.

The complete model structure is presented in Figure 4.

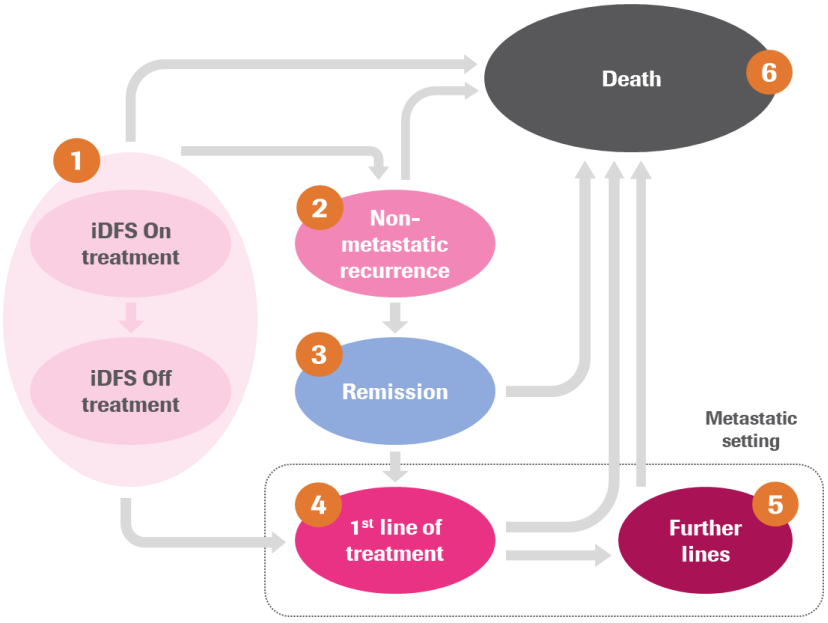

Figure 4 Cost-effectiveness model structure.

The model consists of six health states:

1. Invasive disease progression free survival "IDFS" (making a distinction between patients on and off adjuvant treatment);
2. "Non-metastatic recurrence" (includes locoregional recurrence and contralateral BC);
3. "Remission" (from a non-metastatic recurrence);
4. "First line of treatment in mBC";
5. "Further lines of treatment in mBC" (includes 2nd line of treatment and later lines); and
6. "Death".

The following model transitions are possible:

- All patients “start” from the “IDFS” health state. In this health state, patients are initially on treatment, and then off treatment (after completion of adjuvant therapy). Mean/median/planned time on HER2-directed therapy was about 1 year in both arms This distinction on/off was made as patients may have a different quality of life when receiving treatment (discussed later in the report). In each model cycle (i.e. every month), patients can remain in the IDFS health state or experience an event. This event could be death, a non-metastatic recurrence, or a metastatic recurrence. These three types of events constitute the IDFS definition (primary endpoint) of the APHINITY trial (48) and will determine the subsequent (new) health state to which the patient will transition in the model; either
    - “Death” (1-->6, indicating transition from state 1 to state 6 as in Figure 4);
    - “Non-metastatic recurrence” (1-->2); or
    - “First line of treatment in mBC” (1-->4).

- The “non-metastatic recurrence” (locoregional recurrence and contralateral BC) health state is a tunnel state where patients reside for a year if they do not experience a death event in this period – transitioning to the “death” health state. The duration of the tunnel state was chosen to be maximum 12 months as it is expected that patients in this situation will undergo another episode of adjuvant therapy. After the 12-month period, patients automatically transition to the “remission” health state. See tunnel state in model Excel sheet “PHT” and “HT” in columns AE-BB.

- In the “remission” health state, patients are off treatment and are assumed to have no further sign of the disease (similar to what is in the “IDFS” off treatment health state). In this health state, patients are at risk of death (identical to what is modelled in the “IDFS” health state) and at risk of further metastatic recurrence (with a higher risk than in the “IDFS” health state). It is assumed that patients reaching the “remission” state are not at risk of contralateral or locoregional recurrence anymore o if a patient would develop a second non-metastatic recurrence, the treatment patterns would be like those of a metastatic disease.

- In the “first line of treatment in mBC” health state, the risk of further disease progression (i.e. moving to further lines of treatment in mBC, 4-->5) and the risk of death (4-->6) depend on whether or not the relapse occurs within 18 months of treatment initiation, general population mortality, and (in the case of non-early / late recurrence) the treatment mix observed:

    - in the early metastatic setting monthly transition probabilities to
        - further lines of treatment in mBC are constant, and based on the DESTINY-Breast03 and EMILIA trials (Progression-Free Survival [PFS] data);

        - death depend on general population mortality (age- and gender-adjusted) and the monthly probability of death observed in PFS in the DESTINY-Breast03 (49) or EMILIA (50) trials;

    - in the non-early / late recurrence setting monthly transition probabilities to
        - further lines of treatment and death (here general population mortality [age- and gender-adjusted] is also taken into account) in mBC depend on the treatment patients are expected to receive in this setting:
            - PHT: Perjeta® (pertuzumab) in combination with Herceptin® (trastuzumab) and chemotherapy − based on PFS data of the CLEOPATRA trial (51);
            - HT: Herceptin® (trastuzumab) and chemotherapy – also based on PFS data of the CLEOPATRA trial;
            - Chemotherapy: based on PFS data of the M77001 trial (52);

The treatment mixed observed in the late recurrence setting impacts both costs (see Excel model sheet “Supportive Care Costs” and outcomes (see Excel model sheet “Model Inputs” of the patients.

- Patients that do not remain in the “further lines of treatment in mBC” (includes 2nd line of treatment and later lines) health state can only transition to the “death” health state (5-->6), and do this based, again
    - on whether or not they were early relapsers;
    - general population mortality; and
    - the treatment mix patients received (if applicable) in the non-early recurrence setting.

- “Death” is an absorbing health state, and patients remain in this health state until the model time horizon is reached. As stated above, the risk of death is always adjusted to the background mortality for each health state – to make sure the modelled death rate is at least equal to the death rate observed in the general population adjusted by age and gender.

In the model a transtion from non-metastatic recurrence to metastatic recurrence is not possible, i.e. 2 -> 4. While the potential move between the two health states could in principle occur in reality, Roche deemed it as reasonable to not include this transition for simplification purposes. The model structure has been tested during an advisory board organized in the UK held in September 2017 where the model structure was deemed as appropriate (53). In NICEs assessment of pertuzumab for the adjuvant treatment of HER2-positive early breast cancer the ERG concluded the following regarding the model structure.

In general, the ERG believes that the type and structure of the developed model is appropriate for the purposes of the decision considered in this appraisal. The ERG deems the pathway represented in the model is in line with expectations about the clinical progression of the disease and believes that the structure of the model is suitable to quantify and appraise the costs and health outcomes associated with the compared treatments options (53).

Furthermore no relevant data on the risk of distant recurrence while on treatment for a second early breast cancer was identified.

The main reason for relying on the current modelling approach is that it allows for modelling survival separately in each model state. [redacted] Since the initiation of Aphinity, a number of life-prolonging treatments have become standard of care in Denmark for patients who develop metastatic disease, e.g. Trastuzumab Deruxtecan, Trastuzumab Emtansin and Pertuzumab+trastuzumab+chemotherapy. It is expected that the post-progression survival of patients who experienced metastatic recurrence nowadays would be different from what has been observed in the APHINITY study as the patients may not have received the therapy considered to be the local standard of care today. [redacted]

In high-risk HER2+ eBC, IDFS is a robust surrogate for OS because an IDFS event—specifically distant recurrence—marks the definitive transition from a curable state to an incurable metastatic state. Real world evidence from high-risk populations demonstrates a clear positive correlation between these endpoints: patients with lower 5-year IDFS probabilities (72%) also exhibit lower 5-year OS probabilities (87%) compared to non-high-risk cohorts (Mahtani et al., 2025). This relationship is driven by the aggressive biology of HER2+ disease, where the median time from eBC to metastatic diagnosis (mBC) is only 23 months (54). Once the disease progresses to the metastatic stage, Danish real-world evidence restricts median overall survival to just 37.1 months (Artzi et al., 2023). Therefore, the modeling rationale rests on the fact that improving IDFS directly prevents patients from entering a low-survival metastatic trajectory. Furthermore, utilising IDFS avoids the confounding effects of subsequent lines of therapy and "diluted" survival signals that often occur in OS data due to the long natural history of the disease and high modern efficacy in later lines of care.

Additionally, the APHINITY trial reported a statistically significant reduction in both iDFS and OS. The HR for iDFS at 10 years was 0.74 (95% CI, 0.62–0.88; P = 0.0002) and HR for OS was 0.79 (95% CI: 0.64–0.97). The fact that a simultaneous reduction in risk for both endpoints is observed within the trial provides further credibility of iDFS as a valid surrogate for OS. In addition to the findings of the trial, other studies have found a positive correlation between DFS and OS for patients with HER2+ eBC. Saad et al (55) conducted a meta-analysis of eight trials (n=21480) investigating this matter. The study

concluded that *it is appropriate to continue to use disease-free survival as a surrogate for overall survival in trials in HER-2-positive, early breast cancer* based on the finding that *patient-level associations between diseasefree and overall survival were strong (rs=0·90 [95% CI 0·89–0·90])*.

4.2 Model features

The comparators differ in terms of expected long-term costs and effectiveness. Therefore, we apply a cost-utility analysis. The model features are reported in Table 7.

Table 7 Features of the economic model

Model features	Description	Justification
Patient population	Adult patients with early BC HER2+ ER+	APHINITY study
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Lifetime (52 years)	To capture all health benefits and costs in line with DMC guidelines. Based on mean age at diagnosis in the Danish population (mean 55, range 24-81 years).
Cycle length	A month	Consistent with length of treatment cycle (day 1 every month)
Half-cycle correction	Yes	
Discount rate	3.5 %	A discount rate of 3.5 % in line with DMC guidelines.
Intervention	Phesgo subcutaneous (a combination of Trastuzumab + Pertuzumab) + Chemo Ptz+H+Chemo	APHINITY study
Comparator(s)	Trastuzumab biosimilar IV + Placebo + Chemo Pla+H+Chemo	According to national treatment guidelines. Validated by Danish clinical expert
Outcomes	IDFS (disease free state) and OS	Relevant endpoint within breast cancer

5. Overview of literature

5.1 Literature used for the clinical assessment

This application is based on the head-to-head study, APHINITY (BO25126), which compares pertuzumab plus trastuzumab plus chemotherapy with placebo plus trastuzumab plus chemotherapy as adjuvant therapy in patients with operable HER2-positive primary breast cancer. In Danish clinical practice the comparator used in the APHINITY study reflects the current standard adjuvant treatment in Denmark. Therefore, it is considered a relevant comparator, and a systematic literature review has not been conducted.

Table 8 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*
von Minckwitz G, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med. 2017 Jul 13;377(2):122-131. doi: 10.1056/NEJMoa1703643. Epub 2017 Jun 5. Erratum in: N Engl J Med. 2017 Aug 17;377(7):702. doi: 10.1056/NEJMx170011. Erratum in: N Engl J Med. 2018 Oct 18;379(16):1585. (19)	APHINITY	NCT01358877	Start: 08/11/2011, Completion: 28/11/2024 **Primary Data cut-off 19/12/2016**; secondary Data cut-off 19/06/2019; third Data cut-off: 10/01/2022; Final Data cut-off 28/11/2024. Future data cut-offs: N/A	Pertuzumab plus trastuzumab plus chemotherapy with placebo plus trastuzumab plus chemotherapy as adjuvant therapy in patients with operable HER2-positive primary breast cancer
Piccart M et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer in the APHINITY Trial: 6 Years' Follow-Up. J Clin Oncol. 2021 May 1;39(13):1448-1457. doi: 10.1200/JCO.20.01204. Epub 2021 Feb 4. PMID: 33539215. (56)	APHINITY	NCT01358877	Start: 08/11/2011, Completion: 28/11/2024 Primary Data cut-off 19/12/2016; **secondary Data cut-off 19/06/2019**; third Data cut-off: 10/01/2022; Final Data cut-off 28/11/2024. Future data cut-offs: N/A	Pertuzumab plus trastuzumab plus chemotherapy with placebo plus trastuzumab plus chemotherapy as adjuvant therapy in patients with operable HER2-positive primary breast cancer
Loibl S, et al. Adjuvant Pertuzumab and Trastuzumab in Early Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer in the APHINITY Trial: Third Interim Overall Survival Analysis With Efficacy Update. J Clin Oncol. 2024 Nov;42(31):3643-3651. doi: 10.1200/JCO.23.02505. (48)	APHINITY	NCT01358877	Start: 08/11/2011, completion: 28/11/2024 Primary Data cut-off 19/12/2016; secondary Data cut-off 19/06/2019; **third Data cut-off: 10/01/2022**; Final Data cut-off 28/11/2024. Future data cut-offs: N/A	Pertuzumab plus trastuzumab plus chemotherapy with placebo plus trastuzumab plus chemotherapy as adjuvant therapy in patients with operable HER2-positive primary breast cancer
Loibl, S. et al. Adjuvant pertuzumab or placebo + trastuzumab + chemotherapy (P or Pla + T + CT) in patients (pts) with early HER2-positive operable breast cancer in APHINITY: Final analysis at 11.3 years' median follow-up. ESMO Open, Volume 10, 105112 (24)	APHINITY	NCT01358877	Start: 08/11/2011, Completion: 28/11/2024 Primary Data cut-off 19/12/2016; secondary Data cut-off 19/06/2019; third Data cut-off: 10/01/2022; **Final Data cut-off 28/11/2024**. Future data cut-offs: N/A	Pertuzumab plus trastuzumab plus chemotherapy with placebo plus trastuzumab plus chemotherapy as adjuvant therapy in patients with

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*
				operable HER2-positive primary breast cancer

* 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

Table 9 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Bines, J et al. Patient-reported function, health-related quality of life, and symptoms in APHINITY: pertuzumab plus trastuzumab and chemotherapy in HER2-positive early breast cancer. Br J Cancer 125, 38–47 (2021). https://doi.org/10.1038/s41416-021-01323-y (57)	IDFS (on/off) treatment. Locoregional recurrence. Remission	Section 10, Appendix F
Lloyd A et al. Health state utilities for metastatic breast cancer. Br J Cancer. 2006 Sep 18;95(6):683-90. doi: 10.1038/sj.bjc.6603326. PMID: 16967055; PMCID: PMC2360509. (7)	First and second line metastatic recurrence	Section 10, Appendix F

5.3 Literature used for inputs for the health economic model

In the health economic model, we used data from the following trials, also refer to Table 10 below

- Roche sponsored CLEOPATRA (Clinical Evaluation of Pertuzumab and Trastuzumab) trial
  - Phase III, randomized, double-blind, placebo-controlled trial comparing pertuzumab + trastuzumab + docetaxel vs trastuzumab + docetaxel in HER2-positive metastatic or locally recurrent breast cancer.
- Roche sponsored M77001 trial
  - Phase III, randomized, open-label trial comparing trastuzumab + docetaxel versus docetaxel alone in patients with HER2-positive metastatic breast cancer
- Daiichi Sankyo sponsored DESTINYBreast03
  - Phase III, randomized, open-label trial comparing trastuzumab deruxtecan (T-DXd) vs trastuzumab emtansine (T-DM1) in HER2-positive metastatic breast cancer previously treated with trastuzumab and a taxane
- Roche sponsored EMILIA trial
  - Phase III, randomized, open-label study comparing trastuzumab emtansine (T-DM1) with lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and a taxane

A formal literature search was deemed unnecessary, as CLEOPATRA and M77001 are Roche-sponsored studies investigating Roche's own product, pertuzumab. DESTINY-Breast03 was included in the model since Enhertu represents a newly introduced therapy and no more recent clinical data are available. Data from these studies were utilized exclusively for the model states following IDFS.

EMILIA was a randomised, international, open-label, phase 3 study of men and women aged 18 years or older with HER2-positive unresectable, locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane. Enrolled patients were randomly assigned (1:1) to trastuzumab emtansine (3·6 mg/kg intravenously every 3 weeks) or control (capecitabine 1000 mg/m² self-administered orally twice daily on days 1–14 on each 21-day cycle, plus lapatinib 1250 mg orally once daily on days 1–21).

DB03 was a open-label, randomised, multicentre, phase 3 trial. Patients in the trial were randomly assigned (1:1) to receive trastuzumab deruxtecan 5·4 mg/kg or trastuzumab emtansine 3·6 mg/kg, both administered by intravenous infusion every 3 weeks. Eligible patients had pathologically documented HER2- positive (centrally confirmed) unresectable or metastatic breast cancer that was previously treated with trastuzumab and a taxane in the advanced or metastatic setting or progressed during or within 6 months after neoadjuvant or adjuvant treatment involving trastuzumab and a taxane. Additional eligibility criteria for inclusion in the study were age 18 years or older, an Eastern Cooperative Oncology Group performance status of 0 or 1, and presence of at least one measurable lesion per Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1). Patients were eligible for enrolment in the study if they had clinically inactive or previously treated brain metastases that were no longer symptomatic. For a comparison of the patient population of DB03 versus the relevant patient population in Danish

clinical practice we refer to the DMCs own assessment of T-Dxd for patient with HER+ metastatic disease.

CLEOPATRA was a double-blind, randomised, placebocontrolled, phase 3 trial done at 204 sites in 25 countries. Eligible patients with metastatic, HER2-positive breast cancer were aged 18 years or older, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, left ventricular ejection fraction (LVEF) of at least 50% at baseline, and were naive to previous chemotherapy or biological therapy in terms of treatment for metastatic disease, but could have received chemotherapy with or without trastuzumab in the neoadjuvant or adjuvant settings as long as there was a minimum 12-month interval between completion of all therapy and metastatic disease diagnosis. Patients could have received up to one hormonal treatment for metastatic disease but had no concurrent hormonal therapy before disease progression. Patients were assigned to receive either pertuzumab or placebo at a loading dose of 840 mg, and 420 mg thereafter; plus trastuzumab at 8 mg/kg loading dose and 6 mg/kg thereafter; and docetaxel at 75 mg/m², escalating to 100 mg/m² if tolerated. Pertuzumab or placebo and trastuzumab were given until disease progression; docetaxel was given for six cycles, or longer at the investigators' discretion. Roche views the patient population included in the trial as representative for the relevant patients in Danish clinical practice, considering that the DMC treatment guideline for HER2 positive breast cancer lists Pertuzumab+trastuzumab+chemotherapy as 1st choice in 1st line treatment of metastatic HER2+ breast cancer and CLEOPATRA being the pivotal phase 3 where this treatment was investigated in the relevant patient population.

M77001 was an open-label, comparative, randomized, multicenter, multinational trial comparing the efficacy and safety of first-line trastuzumab plus docetaxel with docetaxel alone in patients with HER2-positive MBC. Patients were enrolled onto the trial in 11 European countries and Australia between April 2000 and October 2002. Patients who had received prior chemotherapy for their metastatic disease or any prior taxanes or anti-HER therapy were excluded. The M77001 trial is used to inform the risk of disease progression and death for patients who only receive chemotherapy as 1L treatment upon developing metastatic disease. In our submitted base-case this is only assumed to be 5.9% of patients who develop metastatic disease as a result of HER2 targeted therapy being the standard of care in 1L metastatic disease for the relevant patient population

Table 10 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
Swain, Sandra M, David Miles, Sung-Bae Kim et al. Pertuzumab, Trastuzumab, and Docetaxel for HER2-Positive Metastatic Breast Cancer (CLEOPATRA): End-of-Study Results from a Double-Blind, Randomised, Placebo-Controlled, Phase 3 Study. The Lancet Oncology 2020;21(4):519–30. (51)	Transition probabilities	N/A	Transition probabilities, Table 24 section 8.1.
Marty, Michel, Francesco Cognetti, Dominique Maraninchi. Randomized Phase II Trial of the Efficacy and Safety of Trastuzumab Combined With Docetaxel in Patients With Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer Administered As First-Line Treatment: The M77001 Study Group.	Transition probabilities	N/A	Transition probabilities, Table 24 section 8.1.

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Journal of Clinical Oncology 2005;23(19):4265–74. (52)			
Cortés et al. Trastuzumab Deruxtecan versus Trastuzumab Emtansine in HER2-Positive Metastatic Breast Cancer: Long-Term Survival Analysis of the DESTINY-Breast03 Trial". Nature Medicine 2024;30(8):2208–15. (58)	Transition probabilities	N/A	Transition probabilities, Table 24 section 8.1.
Diéras, Véronique, David Miles, Sunil Verma, ym. 2017." Trastuzumab Emtansine versus Capecitabine plus Lapatinib in Patients with Previously Treated HER2-Positive Advanced Breast Cancer (EMILIA): A Descriptive Analysis of Final Overall Survival Results from a Randomised, Open-Label, Phase 3 Trial". The Lancet Oncology 18 (6): 732–42. (50)	Transition probabilities	N/A	Transition probabilities, Table 24 section 8.1..

6. Efficacy

6.1 Efficacy of adjuvant pertuzumab plus trastuzumab and chemotherapy compared to trastuzumab plus chemotherapy for patients with HER2-positive, lymph node-positive primary breast cancer

The efficacy chapter of this submission is structured around the N+ patient subgroup, that constituted around 63% of the ITT study population. This population represents the prespecified, clinically relevant high-risk group in which the treatment benefit was most evident and consistent across both IDFS and OS analyses in the APHINITY study.

6.1.1 Relevant studies

The APHINITY study (BO25126) is a pivotal Phase III, prospective, two-arm randomized, multicenter, multinational, double-blind, placebo-controlled study in the adjuvant setting of pertuzumab plus trastuzumab and standard chemotherapy (Ptz+H+Chemo) versus adjuvant placebo plus trastuzumab and standard chemotherapy (Pla+H+Chemo) in patients with operable HER2+ primary BC, the overall study design is presented in Figure 5.

A total of 4805 patients were randomized between 8 November 2011 and 31 August 2013. The Last Patient Last Visit date was 28 November 2024, providing approximately 10 years of follow-up after the last patient completed targeted therapy. Denmark was represented with 9 clinical sites, with a total of 87 Danish patients enrolled in the study.

The primary outcome measure was IDFS (excluding second primary non−breast cancers (SPNBC)). Secondary outcome measures were IDFS including SPNBCs (IDFS-SPNBC), DFS, OS, RFI, DRFI, cardiac safety, overall safety, and HRQoL.
Eligible patients had to have newly diagnosed, primary invasive BC that was HER2+ (overexpressed based on immunohistochemistry [3+] r amplified based on FISH/chromogenic in situ hybridization positive) confirmed by a central pathology laboratory prior to enrollment and had to be suitable for treatment with adjuvant systemic chemotherapy following definitive surgery.

Patients were randomized in a 1:1 ratio to one of two treatment arms, Ptz+H+Chemo or Pla+H+Chemo and stratified according to the following stratification factors:

- Nodal status
- Type of adjuvant chemotherapy regimen (anthracycline-based versus non-anthracycline-based)
- Hormone-receptor status
- Geographical region
- Protocol version (Protocol Version A versus Protocol Version B). Protocol version (A versus B) was introduced as a stratification factor at the time of the first protocol amendment (Version B, dated 20 November 2012).

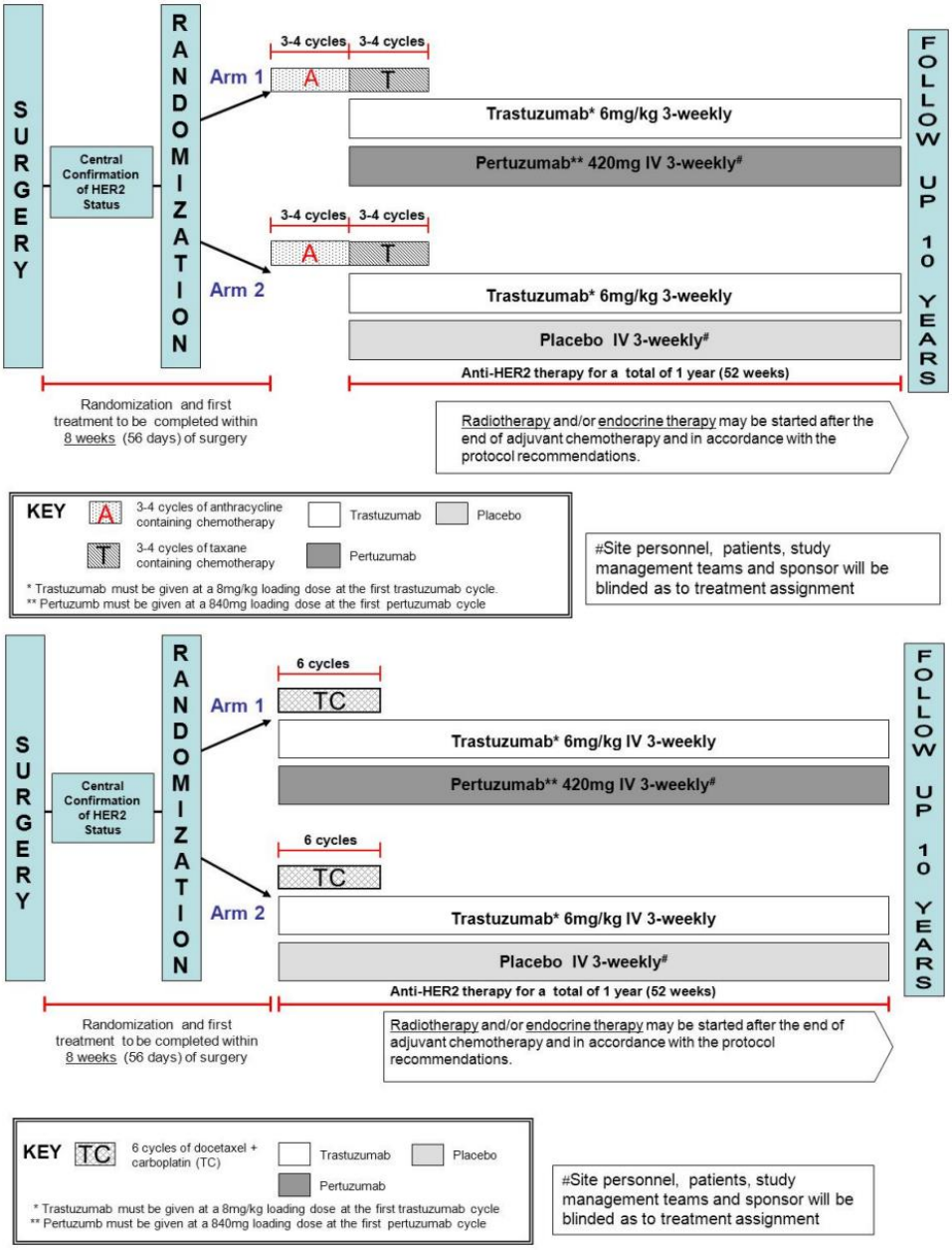

Figure 5 Overview of study design in the APHINITY study (23)

HER2, Human Epidermal Growth Factor Receptor 2.

Table 11 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
APHINITY, NCT 01358877 (19, 24, 43)	A randomized multicenter, double-blind, placebo-controlled phase III trial	Treatment was administered for a total duration of 52 weeks plus a window of 3 days (a maximum of 18 cycles within 1 year).	Patients with operable HER2+ primary BC	**Pertuzumab**: Loading dose 840 mg administered IV followed by 420 mg IV every three weeks (q3w).	**Trastuzumab:** Loading dose 8 mg/kg administered IV followed by 6 mg/kg IV q3w. **Chemotherapy:** Investigators choice of adjuvant chemotherapy for eBC, either with an anthracycline-containing regimen or a non-anthracycline-containing regimen. Administered IV For further details on the chemotherapy regimen dosing see Appendix A	**Primary outcome measures:** Invasive Disease-Free Survival (IDFS), primary analysis for IDFS will take place after patients have been followed for a minimum of 30 months or after 379 events have occurred, whichever occurs later. **Secondary outcome measure:** Overall Survival (OS), Invasive Disease-Free Survival including Second Primary Non-Breast Cancers (IDFS-SPNBC), Recurrence-Free Interval (RFI), Distant Recurrence-Free Interval (DRFI). **Follow-up**: Post treatment, patients were followed at approximately 3 monthly intervals for 2 years, then every 6 months during years 3 to 5 and annually thereafter. Median duration of follow-up for the combined arms at the time of the final analysis (CCOD 28 November 2024) was 135.3 months (11.3 years) The follow-up period and the schedule of assessments were pre-defined in the Protocol BO25126 (23).

BC, breast cancer; DRFI, Distant Recurrence-Free Interval; eBC, early breast cancer, HER2+, Human Epidermal Growth Factor Receptor 2-positive; IDFS, Invasive Disease-Free Survival; q3w, every three weeks; OS, overall survival; RFI, Recurrence-Free Interval; SPNBC, Second Primary Non-Breast Cancers

Data cut-off and respective objectives

The efficacy and safety data presented in the application are based on data from the primary analysis, CCOD of 19 December 2016 and the final OS analysis, CCOD of 28 November 2024. A summary of the CCODs is presented in Table 12.

Table 12 APHINITY study clinical data cut-offs and respective objectives

CCOD	Objectives	Availability
28 Nov 2024	Final OS Analysis, 10 years after last patient completed therapy. Median follow-up 11.25 years. Comprehensive evaluation of long-term efficacy and safety. 452 deaths have occurred 188 less than original target of 640 deaths. Significant improvements in OS were seen in patients with N+ disease HR=0.79 (95% CI 0.64–0.97).	Data on file (43), Poster from ESMO BC 2025 (24, 59)
10 Jan 2022	Third Interim OS Analysis, 5 years after primary analysis. Median follow-up 8 years. 58% of required OS events. OS HR not statistically significant. Trend favoring Ptz+H+Chemo (7.0% vs 8.4% deaths).	Loibl et al 2024 (48), Data on file (60)
19 Jun 2019	Second Interim OS Analysis, 2.5 years after primary analysis. Median follow-up ≈ 6 years from randomization. OS HR=0.85 (95% CI 0.67–1.07). 43% of planned OS events. No statistical significance.	Piccart et al 2020 (56), EMAs assessment report (61), Data on file (62).
19 Dec 2016	Primary analysis, after occurrence of 381 IDFS events. To evaluate IDFS, OS (interim), and secondary endpoints (DRFI, DFS). Median follow-up ≈ 45 months. Study met primary endpoint (HR=0.81, p=0.0446). 19% risk reduction.	Minckwitz et al 2017 (19), EMAs assessment report (61), Data on file (63)

CCOD, clinical cut-off date; CI, confidence interval; DFS, Disease-Free Survival; DRFI, Distant Recurrence-Free Interval; HR, Hazard ratio; N+, node positive; OS, overall survival; Ptz+H+Chemo, pertuzumab+Herceptin (trastuzumab)+Chemotherapy.

6.1.2 Comparability of studies

This section is not relevant as efficacy and safety are compared directly in the APHINITY study.

6.1.2.1 Comparability of patients across studies

Overall, demographic data and baseline disease characteristics were well balanced between the treatment arms and aligned with expectations for the target patient population. Baseline characteristics for the ITT and N+ populations are summarized in Table 13. As the two groups demonstrated comparable baseline profiles, the data will be described only for the N+ populations.

Most patients were White (around 70% in both arms), with a median age of 51 years. More than 99% of patients in each arm were female, with only 8 male patients enrolled in the study in the N+ populations. The distribution of menopausal status was comparable between premenopausal and postmenopausal patients, both across and within the treatment arms. Approximately two-thirds of patients had HR+ or PR+ disease

(63.0% versus 64.2%). The majority of patients received anthracycline-containing adjuvant chemotherapy (80.9% versus 81.2%).

Most patients had fewer than four positive lymph nodes (60.3% versus 59.9%). In the ITT population, approximately 63% of patients had N+ disease.

A protocol amendment (Protocol Version B, dated 20 November 2012) was introduced after 3,655 patients had already been randomized. This amendment restricted enrollment to patients with N+ disease, meaning that patients without nodal involvement were no longer eligible for inclusion in the study. The amendment was implemented in order to enroll a patient population with the nodal-status distribution that had been anticipated when the trial was designed.

Table 13 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	APHINITY (ITT) (19, 63)		APHINITY (N+ cohort)(64)	
	Intervention: Ptz+H+Chemo (n=2400)	**Comparator: Pla+H+Chemo (n=2404)**	**Intervention: Ptz+H+Chemo (n=1503)**	**Comparator: Pla+H+Chemo (n=1502)**
Age, years				
Median (Range)	51 (22–86)	51 (18–85)	51.0 (24-86)	51.0 (19-85)
Age<65	2085 (86.9%)	2111 (87.8%)	1319 (87.7%)	1331 (88.6%)
Age≥65	315 (13.2%)	293 (12.2%)	184 (12.3%)	171 (11.4%)
Gender				
Female	2397 (99.9%)	2396 (99.7%)	1501 (99.9%)	1496 (99.6%)
Male	3 (0.1%)	8 (0.3%)	2 (0.1%)	6 (0.4%)
Race				
White	71.2%	70.5%	69.7%	69.4%
Asian	24.7%	24.9%	26.0%	26.2%
Other	4.1%	4.6%	4.3%	4.5%
Menopausal status at screening	(n=2397)	(n=2395)	(n=1501)	(n=1498)
Pre-menopausal	1152 (48.1%)	1173 (49.0%)	760 (50.6%)	759 (50.7%)
Post menopausal	1242 (51.8%)	1220 (50.9%)	740 (49.3%)	736 (49,2%)
Unknown	3 (0.1%)	2 (<0.1%)	1 (<0.1%)	1 (<0.1%)
BMI (WHO Classification)				
Underweight	53 (2.2%)	57 (2.4%)	37 (2.5%)	26 (1.7%)
Normal	1215 (50.8%)	1210 (50.5%)	737 (49.2%)	753 (50.4%)

	APHINITY (ITT) (19, 63)		APHINITY (N+ cohort)(64)	
	Intervention: Ptz+H+Chemo (n=2400)	**Comparator: Pla+H+Chemo (n=2404)**	**Intervention: Ptz+H+Chemo (n=1503)**	**Comparator: Pla+H+Chemo (n=1502)**
Overweight	719 (30.1%)	673 (28.1%)	462 (30.8%)	416 (27.8%)
Obese	404 (16.9%)	456 (19.0%)	262 (17.5%)	300 (20.1%)
Nodal status				
0 positive nodes and tumor ≤1 cm*	90 (3.8%)	84 (3.5%)	0 (0%)	0 (0%)
0 positive nodes and tumor >1 cm*	807 (33.6%)	818 (34.0%)	0 (0%)	0 (0%)
1-3 positive	907 (37.8%)	900 (37.4%)	907 (60.3%)	900 (59.9%)
>= 4 positive nodes	596 (24.8%)	602 (25.0%)	596 (39.7%)	602 (40.1%)
Adjuvant chemo regimen (randomized)				
Anthracycline	1865 (77.7%)	1877 (78.1%)	1216 (80.9%)	1219 (81.2%)
Non-anthracycline	535 (22.3%)	527 (21.9%)	287 (19.1%)	283 (18.8%)
Hormone receptor status				
Negative (ER and PR negative)	864 (36.0%)	858 (35.7%)	556 (37.0%)	537 (35.8%)
Positive (ER and/or PR positive)	1536 (64.0%)	1546 (64.3%)	947 (63.0%)	965 (64.2%)
Pathologic tumor size (cm)				
Mean (SD)	2.4 (1.5)	2.5 (1.5)	N/A	N/A
Median	2	2	N/A	N/A
Range	0-18	0-14	N/A	N/A
0 – <2	978 (40.8%)	948 (39.4%)	N/A	N/A
≥2 – <5	1275 (53.1%)	1283 (53.3%)	N/A	N/A
≥ 5	147 (6.1%)	174 (7.2%)	N/A	N/A
Protocol version				
Protocol A	1828 (76.2%)	1827 (76.0%)	33 (62.1%)	925 (61.6%)
Protocol Amendment B	572 (23.8)	577 (24.0%)	570 (37.9%)	577 8.4%)

BMI, Body mass index; ER, estrogen receptor; ITT, Intent-To-Treat; N+, node positive; Pla+H+Chemo, Placebo+Herceptin+Chemotherapy; PR, progesterone receptor; Ptz+H+Chemo, Pertuzumab+Herceptin+Chemotherapy; SD, standard deviation.

*Protocol A only

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

Table 14 presents a comparative overview of the N+ population in the APHINITY trial and a corresponding Danish real-world cohort (65). The Danish cohort includes patients with HER2-positive breast cancer and tumours >2 cm and/or node-positive disease who received neoadjuvant chemotherapy with pertuzumab and trastuzumab (65).

Patients with node-positive disease are, both in APHINITY and according to Danish clinical guidelines, classified as high-risk. Therefore, the generalisability of the APHINITY results to Danish clinical practice, particularly regarding the definition of high risk of recurrence, should not be considered a major source of uncertainty in this assessment.

Cohort data was obtained from the DBCG database. This cohort was selected to represent patients at higher risk of recurrence (N+ and/or tumors >2 cm), i.e., the population in which neoadjuvant chemotherapy and dual HER2 blockade is routinely used in Danish clinical practice.

The Danish real-world cohort and the APHINITY population are broadly comparable. Minor differences such as slightly higher mean age (55 vs 51 years), and a lower proportion of premenopausal patients (44% vs 50.7%), are not anticipated to affect the applicability of the treatment effect observed in APHINITY to a Danish population (65).

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

	Value in Danish population (65)	Value used in health economic model (reference if relevant)
Age Mean (range)	55 (24-81) years	51 (24-86) years
Gender (Female)	100 %	99,9 %
Pre-Menopausal	44 %	50.6%
Post-menopausal	-	49.3%
Positive nodal status	41 %	100 %
Adjuvant chemo regimen		
Anthracycline	100%	80.9%
Non-anthracycline	-	19.1%

6.1.4 Efficacy – results per APHINITY (BO25126)

For both the primary endpoint, IDFS, and the key secondary endpoint OS, the numerical differences between treatment groups were most pronounced in the predefined, clinically relevant, N+ high-risk subgroup. Accordingly, the results presented in this

section will focus on the subgroup of patients with N+ diseases, the group of patients that still have an unmet medical need in the eBC setting.

Primary efficacy endpoint

The primary efficacy endpoint IDFS, was defined as the time from randomization until the date of the first occurrence of one of the following events: recurrence of ipsilateral invasive breast tumor, recurrence of ipsilateral locoregional invasive disease, a distant disease recurrence, contralateral invasive breast cancer, or death from any cause. This definition of IDFS (which excludes second primary non-BC as events) differs from the standardized definitions for efficacy end points (STEEP) definition (66).

The stratified log-rank test was used to compare the rates of IDFS between the two treatment groups. The Kaplan-Meier approach was used to estimate 3-year IDFS rates for each treatment group. The stratified Cox proportional-hazards model was used to estimate the hazard ratio (HR) and its 95% confidence interval. The trial was designed to have 80% power to detect a HR of 0.75 at a 5%, two-sided significance level (19).

Invasive Disease–Free Survival (IDFS)

At the time of the primary analysis (CCOD: 19 December 2016), in the subgroup of patients with N+ disease, invasive disease events occurred in 139 patients (9.2%) in the Ptz+H+Chemo group and 181 patients (12.1%) in the Pla+H+Chemo group. The 3-year IDFS rate was 92.0% in the pertuzumab arm and 90.2% in the placebo arm. The HR was 0.77 (95% confidence interval (CI), 0.62–0.96; P = 0.0188), indicating a 23% reduction in risk of recurrence or death in patients receiving Ptz+H+Chemo. The Kaplan-Meier plot is shown in Figure 6.

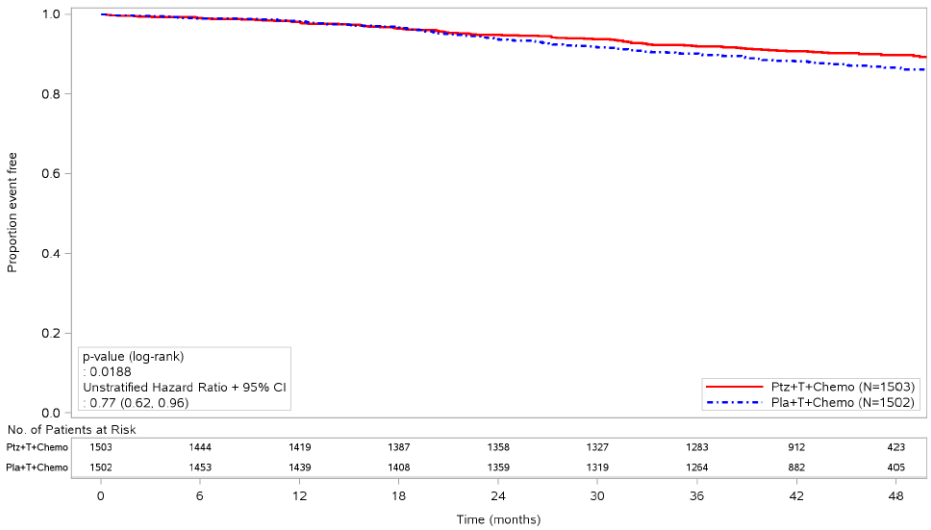

Figure 6 Kaplan-Meier plot of Time to First IDFS Event (months) by treatment regiment, APHINITY, N+ cohort, ITT population. CCOD, 19 December 2016(63).

CI, confidence interval; CCOD, clinical cut-off date; N+, node positive; IDFS, Invasive-Disease–free Survival; Pla+H+Chemo, Placebo+Herceptin+Chemotherapy; Ptz+H+Chemo, Pertuzumab+Herceptin+Chemotherapy

At the time of the final analysis (CCOD: 24 November 2024), after a median follow-up of approximately 11.25 years, invasive disease events were reported in 224 patients (14.9%) in the Ptz+H+Chemo group and 299 patients (19.9%) in the Pla+H+Chemo group.

The 10-year IDFS rate was [redacted] in the Ptz+H+Chemo arm and [redacted] in the Pla+H+Chemo arm. The HR was 0.74 (95% CI, 0.62–0.88; P = 0.0002), indicating a 26% reduction in risk of recurrence or death in patients receiving Ptz+H+Chemo.

The Kaplan-Meier curves (Figure 7) separate early, within the first few years after randomization, and the treatment effect is maintained throughout long-term follow-up, indicating a durable benefit in reducing invasive recurrences. The curves show no late convergence, suggesting sustained disease control among patients receiving pertuzumab (43).

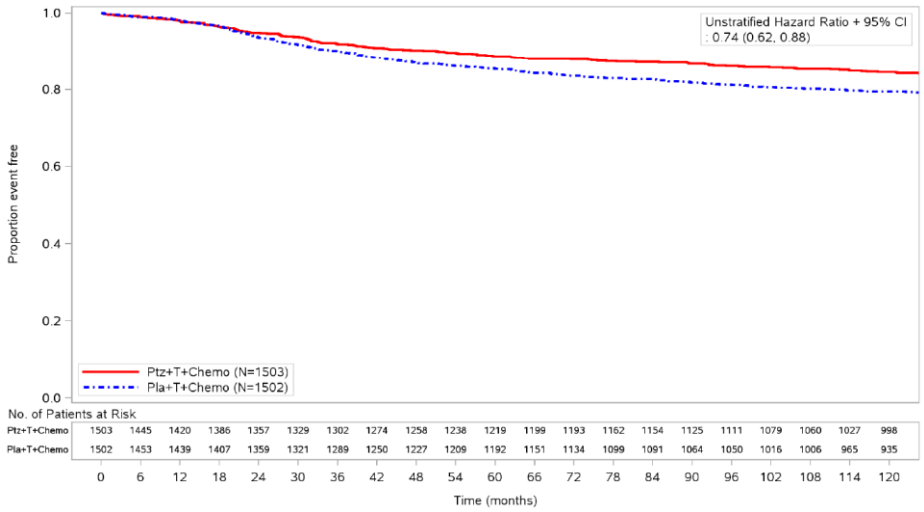

Figure 7 Kaplan-Meier plot of Time to First IDFS Event (months) by treatment regiment, APHINITY, N+ cohort, ITT population. CCOD, 24 November 2024 (43)

CI, confidence interval; CCOD, clinical cut-off date; N+, node positive; IDFS, Invasive-Disease–free Survival; Pla+H+Chemo, Placebo+Herceptin+Chemotherapy; Ptz+H+Chemo, Pertuzumab+Herceptin+Chemotherapy

See Table 16 for an overview of IDFS Event-Free Rates (%) for the N+ population.

Table 15 IDFS Event-Free Rates (%) for the N+ population ((43)

Time point	Ptz+H+Chemo (%)	Pla+H+Chemo (%)
2 Years	[redacted]	[redacted]
3 Years	[redacted]	[redacted]
4 Years	[redacted]	[redacted]
5 Years	[redacted]	[redacted]
6 Years	[redacted]	[redacted]
7 Years	[redacted]	[redacted]
8 Years	[redacted]	[redacted]
9 Years	[redacted]	[redacted]

10 Years	[redacted]	[redacted]

Table 16 Patients with IDFS events in the N+ population (67)

Event Type (First Occurrence)	Ptz+H+Chemo (N=1.503)	Pla+H+Chemo (N=1.502)
Distant Recurrence	[redacted]	[redacted]
Locoregional Recurrence	[redacted]	[redacted]
Contralateral Breast Cancer	[redacted]	[redacted]
Death without prior event	[redacted]	[redacted]
Total Patients with Event	[redacted]	[redacted]

Secondary efficacy endpoint

The analysis of OS for the N+ subgroup was conducted according to the ITT principle using standard time-to-event methodology. OS was defined as the time from randomization to death from any cause. Survival distributions were estimated using the Kaplan-Meier approach, and treatment effects were assessed with a Cox proportional hazards regression model to estimate the HR and 95% CI. Patients without a documented event were censored at the date of last known follow-up.

The subgroup analysis for OS by nodal status was unstratified and considered exploratory. The final OS analysis followed a time-driven design, with the data cut off based on the Last Patient Last Visit date of 28 November 2024, allowing approximately ten years of follow-up after completion of targeted therapy.

The original protocol specified that the final OS analysis would be event-driven, to be conducted once 640 deaths had been reported. During the course of the study, the analysis plan was amended to a time-driven approach.

Overall survival (OS)

At the time of the primary analysis (CCOD: 19 December 2016), the interim OS data was immature, with only 26% of the planned OS events having occurred at the CCOD. Consequently, statistical significance was not reached at that time.

At the time of the final analysis (CCOD: 24 November 2024), patients with N+ disease demonstrated a treatment benefit in favour of Ptz+H+Chemo compared with Pla+H+Chemo.
The 10-year OS event-free rate was 89.55% in the Ptz+H+Chemo arm vs 86.87% in the Pla+H+Chemo arm, corresponding to an absolute difference of 2.68 percentage points.
The HR was 0.79 (95% CI: 0.64–0.97), representing a 21% relative reduction in the risk of death among patients treated with Ptz+H+Chemo compared with Pla+H+Chemo.
The Kaplan-Meier curves showed a sustained separation over time, indicating a consistent treatment effect across the 10-year follow-up period. Median OS was not

reached in either arm, consistent with the expected long-term survival in this adjuvant population. At the time of the final analysis (CCOD: 24 November 2024), a total of 158 OS events (10.5%) were observed in the Ptz+H+Chemo arm compared with 199 OS events (13.2%) in the Pla+H+Chemo arm within the N+ population (67).

These results support a clinically relevant OS benefit in the N+ subgroup, whereas no meaningful effect was observed in N- patients. The corresponding Kaplan-Meier plot of overall survival and OS event-free rates over time is presented in Figure 8.

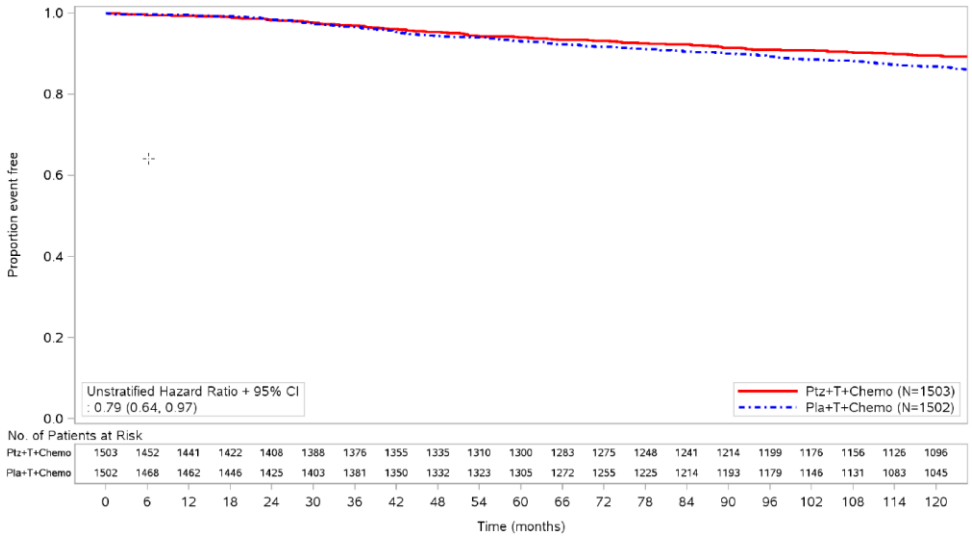

Figure 8 Kaplan-Meier plot of OS by treatment regiment, APHINITY, N+ cohort, ITT population: CCOD, 24 November 2024 (43)

CI, confidence interval; CCOD, clinical cut-off date; N+, node positive; OS, overall survival; Pla+H+Chemo, Placebo+Herceptin+Chemotherapy; Ptz+H+Chemo, Pertuzumab+Herceptin+Chemotherapy

7. Comparative analyses of efficacy

N/A, since comparisons are based on a head-to-head study. Table 17 is completed with results from APHINITY.

7.1.1 Differences in definitions of outcomes between studies

N/A

7.1.2 Method of synthesis

N/A

7.1.3 Results from the comparative analysis

Table 17 Results from the comparative analysis of Ptz+H+Chemo vs. Pla+H+Chemo for patients with HER2+, N+ primary BC (43, 63)

Outcome measure	Ptz+H+Chemo (N=1503)	Pla+H+Chemo (N=1502)	Result
IDFS 3-years rate	92.0% (90.59, 93.40)	90.2% (88.63, 91.69)	1.8% HR: 0.77 (95% CI: 0.62, 0.96; p = 0.02)
IDFS 10-years rate	84.58% (82.68, 86.49)	79.55% (77.43, 81.67)	5.04% HR: 0.74 (95% CI: 0.62, 0.88; p = 0.006)
OS 10-years rate	89.55% (97.93, 91.17)	86.87% (85.08, 88.66)	2.68% HR: 0.79 (95% CI: 0.64, 0.79; p = 0.0261)

CI, confidence interval; CCOD, clinical cut-off date; HR, Hazard ration; IDFS, Invasive Disease-Free Survival; N+, node positive; OS, Overall survival; Pla+H+Chemo, Placebo+Herceptin+Chemotherapy; Ptz+H+Chemo, Pertuzumab+Herceptin+Chemotherapy

7.1.4 Efficacy – results per [outcome measure]

N/A

8. Modelling of efficacy in the health economic analysis

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

8.1.1 Extrapolation of efficacy data

8.1.1.1 Extrapolation of IDFS

Assessment of invasive disease-free survival

Efficacy data are based on the most recent data cut CCOD 28 November 2024 from the APHINITY clinical study. Median follow-up time was 11.3 years (135.3 months) for the combined arms. Extrapolation beyond the clinical follow-up period was performed only for IDFS by fitting parametric distributions to the observed time to event data from the trial. So empirical data from the observed APHINITY study was used directly incorporating Kaplan Meier (KM) data from APHINITY to estimate IDFS up to the follow-up period.

For Time to off treatment (TTOT), no extrapolation was needed as time on treatment had been observed at the time of the data cut. Likewise, the OS data from the trial is neither extrapolated nor fitted. The OS data is modeled using monthly transition probabilities based on the patient's disease status (IDFS, remission, non-metastatic recurrence, metastatic recurrence) and treatment type.

The following steps were used to select the most relevant extrapolation for IDFS:

1. Visual inspection of the IDFS log-cumulative hazard plots, Schoenfeld test and smoothed hazard functions, based on patient level data for the two arms of

APHINITY, to test for the plausibility of the proportional hazards assumption and to examine the hazard of progression or death in each arm over time.

2. The Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) goodness-of-fit statistics were calculated to assess statistical fit of the models to both arms of the IDFS KM data from APHINITY.

3. The clinical plausibility of the long-term extrapolations for the base case parametric models was validated by comparing the long-term behavior of the models with suitable data sources, natural history of the disease (mortality), previous submissions and the expectations of clinical experts.

Six parametric distributions were fitted to the existing IDFS data in order to extrapolate it beyond the observation period: exponential, Weibull, Gompertz, log-normal, generalized gamma and log-logistic distributions. The Gamma distribution is mathematically a restricted form of the Generalized Gamma and adds only little in terms of model diversity, so gamma was excluded in the model engine.

IDFS was a primary endpoint in the APHINITY clinical trial. In the long-term analysis, the IDFS benefit observed with (Phesgo) Ptz+H+Chemo at the primary analysis was maintained in the ITT population with extended follow-up. Treatment with Ptz+H+Chemo demonstrated a numerical improvement in IDFS compared with its comparator Pla+H+Chemo (HR = 0.79, 95% CI 0.68, 0.92), representing a 21% reduction in the relative risk of relapse or death. Ten years from randomisation, estimates of IDFS event-free rates were 87.17% for Ptz+H+Chemo versus 83.82% for Pla+H+Chemo.

In the node-positive subgroup, where the treatment benefit was most apparent at the primary analysis, the hazard ratio for IDFS was 0.74 (95% CI 0.62, 0.88). Ten years from randomisation, estimates of IDFS event-free rates were [redacted] in the Ptz+H+Chemo arm compared with [redacted] in the Pla+H+Chemo arm.

Assessment of proportional hazards (PH)

The economic evaluation is based on the most up to date data cut from APHINITY (CCOD: 28 November 2024). Extrapolation beyond the APHINITY clinical follow-up period was needed and performed by fitting parametric distributions to the observed data (parametric survival analysis) to assess long-term / lifetime impacts of the treatments. The IDFS KM curves for Ptz+H+Chemo vs Pla+H+Chemo (Figure 9) demonstrate a reduced progression risk for patients treated with Ptz+H+Chemo vs Pla+H+Chemo.

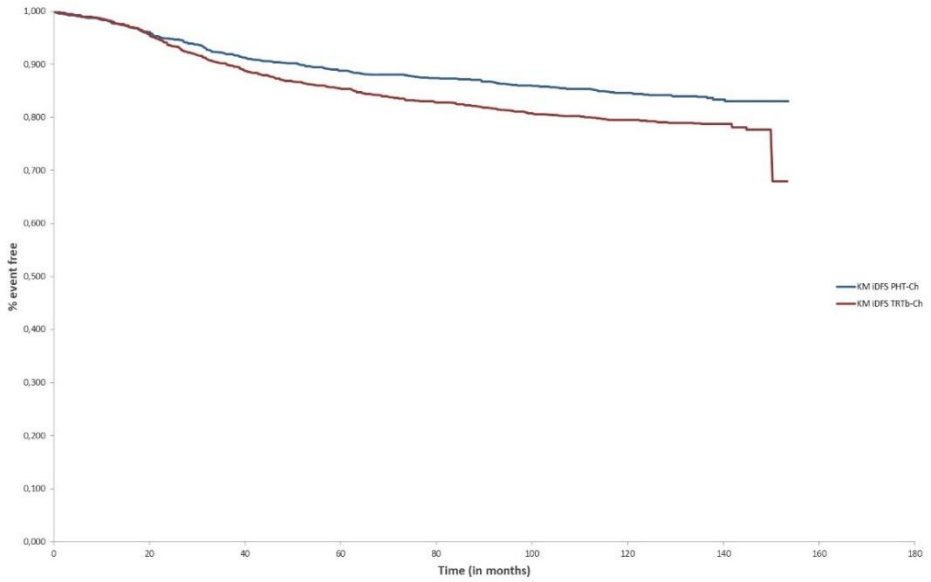

Figure 9 IDFS KM curves for Ptz+H+Chemo and Pla+H+Chemo

IDFS, Invasive Disease-Free Survival; KM, Kaplan-Meier; Pla+H+Chemo, Placebo+Herceptin+Chemotherapy; Ptz+H+Chemo, Pertuzumab+Herceptin+Chemotherapy

The first step in selecting an appropriate extrapolation model is to verify whether the proportional hazards (PH) assumption holds for IDFS. This can be assessed using the Schoenfeld test, by plotting the log-log plot of survival and exploring (smoothed) hazard rate.

The cumulative hazard functions for both treatment arms in the APHINITY trial were plotted on a log-cumulative hazard scale (log of the negative log of the survival function against log time). If the PH assumption is valid, the two curves in the log-log survival plot should be approximately parallel. However, as illustrated in Appendix D.1.3 Figure 21, the curves intersect at multiple time points, suggesting that the PH assumption does not hold. On the other hand, the Schoenfeld test (p = 0.49) in Appendix D.1.3 Figure 22 indicates that there is no strong evidence of time-varying effects, so the proportional hazards assumption appears valid. Whereas smoothed hazard functions (Appendix D.1.3 Figure 23) indicate change over time in shape. Hence the hazard ratio does not seem to be constant and the relative risk between groups appears to vary over time.

The Schoenfeld test would allow acceptance of the proportional hazard assumption but based om log-log survival plot and smoothed hazard functions, we assume the PH assumption is violated.

Statistical fit of models to the observed data

Table 55 in the Appendix D.1.4 summarizes the AIC and BIC values for each extrapolation, with a lower AIC or BIC value indicating a better fitting model. The Gompertz distribution is clearly considered to be the best fit using AIC and BIC criteria for both Ptz+H+Chemo vs Pla+H+Chemo. Log-normal distribution was the second highest ranked distribution for both Ptz+H+Chemo vs Pla+H+Chemo. Several distributions, such as the exponential, exhibited a poor fit to the observed data and generated implausible long-term survival extrapolations.

APHINITY study provides us with a substantial follow-up time to rule out the events related to disease. Extrapolation for the lifetime horizon bears uncertainty about the exact shape of the curves. The quality and plausibility of the extrapolation beyond the observed data is assessed in the next sub-section.

Clinical plausibility of long-term extrapolations for IDFS

A visual inspection shows that the Gompertz distribution provides a significantly better fit to the data for both treatment arms compared to other distributions (Appendix D.1.6 Figure 24). While Gompertz is typically not favored as an overall fit in survival model due to its tendency to produce implausible long-term survival predictions (characterized by a long flat tail), this limitation is mitigated in this case.

The long-term survival outcomes of patients having early breast cancer are influenced by cure and treatment effects, as well as background mortality, with these factors modeled as transition probabilities. These adjustments (explained in Section 8.1.3) work together to shape the long-term survival projections and reduce the uncertainty associated with using the Gompertz distribution in this context.

To have a better fit with the observed study data during the initial months of the study, the model also uses the KM data directly to inform the IDFS survival until the time point when parametric fitting is applied. As such, the reference case presented in the model uses the "KM with Gompertz tail" distribution option. This option allows potentially constant survival for consecutive model cycles that is a consequence of using the non-parametric KM estimate. However, the difference between fully parametric with Gompertz and extrapolation with KM with Gompertz tail approaches is marginal (see sensitivity analysis section).

With the current model settings, from 156 months onwards the modeled IDFS curve will mostly follow that of the general background mortality in the population as patients are assumed to be cured (see Section 8.3). Hence the choice of parametric distribution will have a smaller impact in this economic evaluation than usual (see sensitivity analysis).

Table 18 Summary of assumptions associated with extrapolation of IDFS

Method/approach	Description/assumption
Data input	APHINITY study
Model	KM with Gompertz tail.
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	Intervention: Gompertz function Comparator: Gompertz function
Function with best BIC fit	Intervention: Gompertz function Comparator: Gompertz function

Method/approach	Description/assumption
Function with best visual fit	Intervention: Gompertz function Comparator: Gompertz function
Function with best fit according to evaluation of smoothed hazard assumptions	Intervention: Gompertz function Comparator: Gompertz function
Validation of selected extrapolated curves (external evidence)	Clinical experts' opinions on clinical plausibility
Function with the best fit according to external evidence	Intervention: Gompertz function Comparator: Gompertz function
Selected parametric function in base case analysis	Intervention: Gompertz function (KM with Gompertz tail) Comparator: Gompertz function (KM with Gompertz tail)
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	Yes
Assumptions of cure point	Yes

KM, Kaplan-Meier

8.1.1.2 Extrapolation of [effect measure 2]

N/A

8.1.2 Calculation of transition probabilities - general principles

We applied time-varying transition probabilities (IDFS curve from the APHINITY study) and constant transition probabilities (exponential) for post-recurrence / metastatic transition. Extrapolation beyond the clinical follow-up period was performed by fitting parametric distributions to the observed time to event data from the trial for the IDFS curve.

OS was modelled by estimating the risk of death in each health state of the model. While a patient resides in the "IDFS" health state, they are assigned the risk of death observed in the general population. It is assumed that the disease will worsen before the patient dies from it. A patient will experience disease progression (e.g., moving to "non-metastatic recurrence" or "metastatic recurrence") before dying from cancer. Thus, deaths specifically attributable to cancer are only modeled to occur after the disease has progressed into more advanced stages while in the "IDFS" state, the risk of death is aligned with the mortality rates of the general population, as derived from life tables available in the Excel model. The resulting modeled death rate is always higher or equal

to the general background mortality. Transition probabilities for OS were modelled using the monthly transition probabilities based on the disease status of a patient and the type of treatment they receive derived from literature / other trials.

8.1.3 Modeling of Transition Probabilities

Early Time-Dependent TPs for IDFS

This initial phase models the movement of patients out of the "Invasive Disease-Free Survival" (IDFS) state, the period immediately following adjuvant therapy when the risk of cancer recurrence is highest and the benefits of treatment are active.

Time dependent state transitions are based on the KM survival data from the APHINITY trial, specifically the IDFS endpoint for the node-positive subgroup. For the first 100 months we apply KM curve and after that tail with the specific distribution (Gompertz as defined earlier). So, until this point, the empirical KM curve is used and after this time point, event probabilities are applied to the last KM PFS estimate. Parametric curve is applied at this time point to stabilise the uncertainty related to tail of the KM curve. Percentage of (any) event free patient are described in Figure 10 and Figure 11.

Figure 10 KM with Gompertz tail distribution – Intervention

IDFS, Invasive Disease-Free Survival; KM, Kaplan-Meier; PHT-Ch, Pertuzumab+trastuzumab + chemotherapy

Figure 11 KM with Gompertz tail distribution – Comparator

IDFS, Invasive Disease-Free Survival; KM, Kaplan-Meier; TRTb-Ch, trastuzumab biosimilar + chemotherapy

Time-Varying adjustments in IDFS state

Waning effect

In economic evaluations various treatment effect waning assumptions can be applied to the intervention during IDFS state. This means in the context of this submission that the hazard of the intervention would gradually and linearly decrease to the level of comparator's hazard. The inclusion of treatment waning is used in order to reduce the uncertainty associated with extrapolation. However, the waning assumption and its starting and stopping parameters are rather arbitrary and typically difficult to justify unequivocally based on clinical evidence.

As observable data (APHINITY trial) is available for 11.3 years / 136 months (median follow up). The time point at which treatment effect (hazard) starts to decrease in the reference case is 120 months to include all observable data and treatment effect is considered to wane over a period of three years (36 months), consistent with previous Roche models of the intervention. So, the treatment effect is slowly fading away until it is at the level of comparator's hazard at 156 months (month 120 + 36 months).

Cure proportion

In the model it is assumed that patients are (almost) no longer at risk of having a disease recurrence at 120 months after treatment initiation. This applies as cure proportion adjustment in the model. Similarly to the waning effect, the time at which the cure proportion starts is set to 120 months to utilize the information from the empirical data. Maximum cure proportion, similarly, is reached after 3 years consistent with previous Roche models and is reached at 156 months. Although it is possible to set the cure and duration of treatment effect assumptions to start for instance from 96-132 months, this will mean a more rapid adjustment that visually may create an IDFS curve that appears less clinically plausible. Cure proportion was used because otherwise the model may produce too conservative estimates in terms of IDFS risk compared to real life.

Roche's view is that any cure and duration of treatment effect assumptions should not reach their maximum any earlier than the observable data maximum follow up to 156 months. This is to avoid that the IDFS survival is tweaked during the observable study data period where we already have high quality data from the APHINITY study available. Similarly, starting the adjustments, any earlier may make the goodness of fit tests (AIC and BIC) incorrect. This adjustment ensures that after 10 years, only background mortality applies and there is no excess risk for recurrence of the disease. Moreover, consistency between the starting and stopping points of the waning and cure assumptions should be maintained. Further argumentation regarding the assumption of a cure point can be found in section D.1.11 *Non-metastatic recurrence*

Transition from IDFS to recurrence states (1-->2; 1-->4) is based on monthly event probability and is split using the fixed proportions observed in APHINITY for proportion of metastatic recurrence and non-metastatic recurrence for early and late relapser (see model sheet "IDFS Events"). Proportions are the same both intervention and comparator. For early relapser the proportion of metastatic recurrence is [redacted] and proportion of non-metastatic recurrence is [redacted] For late relapser the proportion of metastatic recurrence is [redacted] and proportion of non-metastatic recurrence is [redacted] Patients experiencing early disease recurrence (<18 months) in IDFS state can only transition to the metastatic setting (1-->4) in order to reflect their worse prognosis post-progression.

So the proportion between non-metastatic and metastatic disease is used in the model to divide patients leaving the IDFS state between non-metastatic recurrence health state (1-->2) and first line of treatment in mBC (1-->4). Practically the probability of transition to non-metastatic state (1-->2) is derived from trial IDFS data by first removing deaths from the total IDFS events to isolate non-death recurrences. These are then adjusted for patients remaining at risk and split into metastatic and non-metastatic outcomes using trial-based proportions (varying by early vs. late recurrence).

As described in section 4.1, all patients who experienced a non-metastatic recurrence would undergo one year of treatment for exactly 12 months if not death in that period and then enter the remission state afterwards (2-->3). Patients are at risk of death (based on the background mortality) during this year (2-->6).

The monthly transition probability from the non-metastatic (recurrence-free) state to death (2-->6) was derived from the APHINITY clinical trial by dividing the number of deaths without prior recurrence or metastasis by the cumulative patient time at risk across all patients (i.e., [redacted] over 405 675 patient-months), resulting in a monthly probability of [redacted]. In the model, this disease-related death probability is applied to patients in the non-metastatic health state. However, to ensure that overall mortality in this state does not fall below the expected background mortality of the general population, the model takes the maximum of the disease-specific probability ([redacted]) and the age-specific all-cause mortality obtained from national life tables (see model tabs “General Mortality” and Life Tables”.

Transition from remission

Once the patient has experienced a locoregional recurrence, it is assumed that the following recurrence (if any) would be metastatic and treated as a metastatic recurrence. The risk of a second malignancy, i.e. (monthly probability of subsequent metastatic recurrence in the model (3-->4) is based on Hamilton et al. (68). This study included a cohort of 12,836 early breast cancer patients and estimated the risk of a second malignancy after adjuvant therapy. The mean time until the progression was 7.6 years; this value was converted into a monthly transition probability of 0.76%. There are differences between the populations described in the model and the one in the publication. The impact of the value of this transition was therefore explored in a sensitivity analysis.

A constant recurrence rate was assumed over time. Therefore, an exponential distribution could be used to model the survival probability over time. Median survival (i.e. 50% survival) at 7.6 years (91.2 months) translates into the following equation:

$S(t) = e^{-\varphi t}$, where t is time and φ is the hazard rate. Then,

$S(91.2) = 0.5 = e^{-91.2\varphi}$ then, $\varphi = 0.0076$

Transition from "Remission" to "Death" (3-->6) is calculated similarly as from "Non-metastatic recurrence" to "Death" (2-->6). Model takes the maximum of the disease-specific probability (0.00023) and the age-specific all-cause mortality obtained from national life tables (see model tabs “General Mortality” and Life Tables”.

Metastatic disease in early relapsers

For the metastatic disease the model uses other clinical trial data. The DESTINY-Breast03 phase 3 clinical trial examined the effect of trastuzumab deruxtecan (T-Dxd, Enhertu) versus trastuzumab emtansine (T-DM1, Kadcyla) in adult patients with HER2-positive unresectable or metastatic breast cancer previously treated with trastuzumab and a taxane (49). The trial was done in 169 study centres in North America, Asia, Europe, Australia, and South America in a total of 524 patients (261 on T-Dxd and 263 on T-DM1). Updated results of this trial were reported by Cortes et al (2024)(58) on the data with cut-off date 23 June 2020. The median follow-up was 28.4 months with T-Dxd and 26.5 months with T-DM1.

The observed median progression-free survival by blinded independent central review was 28.8 months (95% CI: 22.4–37.9) with trastuzumab deruxtecan and 6.8 months (95% CI: 5.6–8.2) with trastuzumab emtansine. The resulting hazard ratio (HR) is 0.33 (95% CI: 0.26–0.43, p<0.0001).

The median overall survival was not reached (95% CI: 40.5 months–not estimable), with 72 (28%) overall survival events in the trastuzumab deruxtecan group and was not reached (95% CI: 34.0 months–not estimable), with 97 (37%) overall survival events in the trastuzumab emtansine group. The resulting hazard ratio for overall survival is 0.64 (95% CI: 0.47–0.87], p=0.0037).

Table 19 Hazard ratio of trastuzumab deruxtecan versus trastuzumab emtansine, DESTINY-Breast03 (CCOD June 20)

Outcome measure	Hazard ratio	Lower 95% CI	Upper 95% CI
Overall Survival	0.64	0.47	0.87
Progression-free survival	0.33	0.26	0.43

CI, Confidence Interval

As Enhertu is (or will become in the near future) the standard of care for first line metastatic early relapsers and for second line treatment of metastatic late relapsers, the model was adapted to incorporate the effect of the treatment as well (rather than only the costs). To do this, the following monthly transition probabilities were adapted using the hazard ratios reported.

1. In the early metastatic setting
    a. Progression of first line metastatic patients (4-->5)
    b. Death of first line metastatic patients (4-->6)
    c. Death of second line metastatic patients (5-->6)
2. In the late metastatic setting – per treatment
    a. Death of second line metastatic patients (5-->6)

The previous Roche PTH-models have used the EMILIA pooled trial data for the monthly transition probabilities in the early setting. This to take into account that a mix of treatments was given, not only Kadcyla. In the updated clinical practice, as estimated by

Roche, the treatment is now a mix of Enhertu and clinical trials. To estimate the probability of progression, the hazard ratio of PFS 0.33 is applied to the EMILIA pooled data. For the probability of death, the OS HR 0.64 is applied to the EMILIA pooled data.

For the late metastatic setting, the probability of dying per treatment is used. For the monthly probability of death for patients on Enhertu, the OS HR observed in DESTINY-Breast03 is applied to the monthly probability of death for patients on Kadcyla.

The resulting monthly transition probabilities added to the model, used as basecase and are presented in Table 20 and are are available in model sheet "ITC_Enhertu".

For the progression within the metastatic health states, i.e. 4->5, where PFS data is used the model utilizes a methodological decomposition approach to estimate transition probabilities. This means that “PFS” has been censored for death, and deaths while in PFS state are used to derive the death transitions.

Table 20 Estimated monthly transition probabilities in the metastatic setting incorporating Enhertu

Early metastatic setting	EMILIA pooled data	HR applied	Estimate for clinical practice including Enhertu (base case in the model)
"1st line metastatic" to "2nd line+ metastatic" (4-->5)	0.0696	0.33	0.02352
"1st line metastatic" to "Death" (4-->6)	0.0040	0.64	0.00256
"2nd line+ metastatic setting" to "Death"(5-->6)	0.0525	0.64	0.03394
Late metastatic setting	**Kadcyla (EMILIA)**	**HR applied**	**Estimate for Enhertu**
"2nd line+ metastatic setting" to "Death" *	0.0211	0.64	0.01355

* Only used in calculating treatment weighted probability of metastatic death
HR, Hazard ratio

Modelling of metastatic disease in late relapsers

The risk of disease progression and death in the metastatic setting (recurrence observed at least 18 months after treatment initiation) has largely changed in the past ~7 years. This is due to new therapies becoming available, thereby increasing survival for patients with HER2 positive mBC including Perjeta® in 1st line setting and Kadcyla® in 2nd or 3rd line setting. It is expected that the post-progression survival of patients who experienced metastatic recurrence nowadays would be different from what was originally observed in the APHINITY study as the patients may not have received the therapy considered to be the local standard of care today.

The risk of disease progression and death in metastatic setting has then been estimated considering the therapies a patient with a metastatic disease will receive today in Denmark and adjusted to the market share observed locally (as opposed to what was observed in APHINITY).

The risk of disease progression and the risk of death have been extrapolated using the available evidence on these treatment regimens in the metastatic setting:

- For PHT and HT the risk of disease progression (i.e. moving from "1st line mBC" to "further lines mBC") and the risk of death post-progression (i.e. moving from "further lines mBC" to "Death") have been derived from the CLEOPATRA trial data (69) (see model sheet "1st line data")
- For chemotherapy, the risk of disease progression and the risk of death post-progression is derived from the M77001 trial (70) (see model sheet "1st line data").

To avoid the use of time-dependent transition probabilities and to keep the model complexity at a reasonable level, the KM data from these trials have been extrapolated using an exponential distribution (information available in the Excel model in sheets "1st line data" and "2nd line data"). Although visually not the best parametric fit, the average survival predicted by the exponential extrapolation is similar to the truncated survival predicted with the KM estimates only (Table 21).

Table 21: Comparison of KM estimates and extrapolated (exponential) estimates (same time horizon)

Months	KM estimates	Exponential extrapolation	Data source
PFS – pertuzumab	28.0	28.4	CLEOPATRA
PFS – trastuzumab	20.8	21.1	CLEOPATRA
PFS – chemotherapy	14.9	15.6	M77001
PPS – pertuzumab	29.9	30.7	CLEOPATRA
PPS – trastuzumab	19.4	18.6	CLEOPATRA
PPS – chemotherapy	13.9	15.3	M77001

PFS, Progression-Free survival; PPS, Post-progression Survival

It is assumed that while in the "1st line mBC" setting the risk of death is modelled by using the maximum number of deaths without progression events observed in the studies mentioned previously and the general population mortality, in practice, the general population mortality is the higher of the two as patients usually progress before dying from the disease.

Risk of disease progression in 1st line metastatic setting, risk of death in 1st line metastatic setting and risk of death in 2nd line metastatic setting and the data from CLEOPATRA and M77001 (incl. exponential extrapolation parameters) are available in the model (see sheets "1st line data" and "2nd line data"). Once in metastatic setting, the risk of recurrence depends also on the treatment the patient receives (see model sheet “Model Inputs”).

Treatment assumed for first line, provided in Table 22 are sourced from the ESTHER database (71), which investigated treatment patterns for patients with HER2+ metastatic breast cancer in the UK. The division was deemed as representable for Danish clinical practice. Treatment mix in Table 23 is an assumption based on an assessment of the DMC treatment guidelines for HER2 positive breast cancer

Table 22 First line metastatic monthly probability of progression and death used in the model

	% treatment mix** in first line metastatic setting (weighting factor)	Monthly probability of disease progression in 1st line metastatic (4-->5)	Monthly probability of death in 1st line metastatic disease (4-->6)
Perjeta + trastuzumab + chemotherapy	71.2%	0.0312	0.0016
trastuzumab + chemotherapy	22.9%	0.0459	0.0037
chemotherapy	5.9%	0.0670	0.0231
TOTAL (weighted)	100%	0.0367	0.00335*

* If background mortality is higher, then background mortality applies
** Source of treatment mix: ESTHER trial (71)

Table 23 Second line metastatic monthly probability of death

	% treatment mix in second line metastatic setting (weighting factor) *	Monthly probability of death in second line metastatic disease (5-->6)
trastuzumab + chemotherapy	20%	0.0310
Enhertu	80%	0.0135
TOTAL (weighted)	100%	0.01704

*Assumed treatment mix is an assumption based on the DMC treatment guidelines for HER2 positive breast cancer

All constant transition probabilities and their sources are described in Table 24 (excluding Death) and in Figure 12 (excluding time-dependent data derived from APHINITY). Probabilities in Figure 12 occur for both the intervention and comparator.

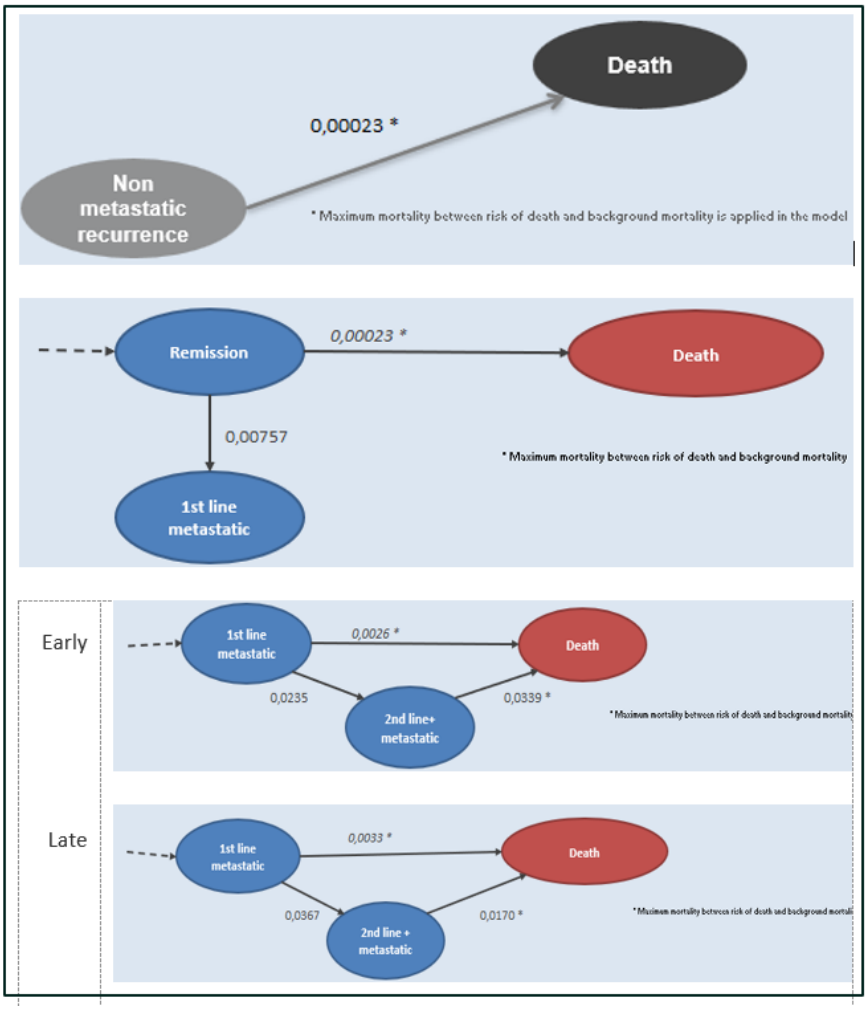

Figure 12 Constant state transition probabilities for health states after IDFS
IDFS, Invasive Disease-Free Survival

Table 24 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
IDFS	Non-metastatic Recurrence	Survival function, parametric extrapolation	APHINITY
	1st treatment line mBC	Survival function, parametric extrapolation	APHINITY
	Death	Death in IDFS	APHINITY (all treatment arms)
Non-metastatic recurrence	Remission	Remission after 12 months tunnel state	APHINITY (all treatment arms)
	Death	Death in IDFS	APHINITY (all treatment arms)

Remission	1st treatment line mBC	Risk of a second malignancy after adjuvant therapy	Hamilton et al.
	Death	Death in IDFS	APHINITY (all treatment arms)
1st treatment line mBC (early disease recurrence)	Subsequent treatment lines mBC	Derived from the PFS data of the EMILIA trial	EMILIA trial
	Death	Enhertu estimate	DESTINY-Breast03
1st treatment line mBC (late disease recurrence)	Subsequent treatment lines mBC	Risk of deaths in PFS	CLEOPATRA
	Death	Risk of deaths in PFS	CLEOPATRA
Subsequent treatment lines mBC	Death	Risk of deaths in PFS	CLEOPATRA; M77001

IDFS, Invasive Disease-Free Survival; mBC, metastacic breast cancer; PFS, Progression-Free-Survival

8.2 Presentation of efficacy data from [additional documentation]

N/A

8.3 Modelling effects of subsequent treatments

The clinical effects of potential subsequent treatments are modelled using the transition probabilities described in chapter 8.1. Effects of subsequent treatment do not differ between intervention and comparator, and the same transition probabilities are used.

8.4 Other assumptions regarding efficacy in the model

Background mortality was calculated using age- and gender-specific all-cause mortality rates (life tables) by year in the general Danish population, obtained from the DMC Mortality sheet. Sex-adjusted 1-year mortality rates were calculated from this source, adjusted by the relevant cohort sex distribution.

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

In APHINITY, most of the patients ([redacted]% in treatment arm and [redacted]% in the comparator arm) completed the episode of care as per protocol (i.e. they were not censored from the trial - Table 25). Therefore, APHINITY can be seen as an accurate data source for

treatment duration, and therefore for Time to off treatment (TTOT), no extrapolation was needed as time on treatment had been observed at the time of the data cut.

Table 25 Patient disposition during treatment period by treatment regimen (randomized patients) (63)

	Intervention N = 2400	Comparator N = 2404
Completed intervention/ comparator treatment	[redacted]	[redacted]
Discontinuation due to safety	[redacted]	[redacted]
Discontinuation for other reason	[redacted]	[redacted]

In the reference case, the observed treatment duration is used for targeted therapies. For chemotherapy, only the option per label is available. This is not expected to have an impact on model outcomes, as chemotherapy use across treatment arms is similar, and costs of chemotherapy are low compared to targeted therapies.

Table 26 Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
Ptz+H+Chemo	[redacted]	N/A	[redacted]
Pla+H+Chemo	[redacted]	N/A	[redacted]

In Table 27 the modelled average treatment length and time is described.

Table 27 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length, months	Median IDFS, months	Mean IDFS, months
Ptz+H+Chemo	[redacted]	[redacted]	[redacted]
Pla+H+Chemo	[redacted]	[redacted]	[redacted]

IDFS, Invasive Disease-Free Survival; Pla+H+Chemo, Placebo+Herceptin+Chemotherapy; Ptz+H+Chemo, Pertuzumab+Herceptin+Chemotherapy

9. Safety

9.1 Safety data from the clinical documentation

In the APHINITY study safety as evaluated as a secondary endpoint with the following objectives:

- Incidence of a symptomatic ejection fraction decrease (defined as heart failure) or definite or probable cardiac death
- Incidence of asymptomatic left ventricular systolic dysfunction (LVSD) (defined as an absolute decrease in left Ventricular Ejection Fraction (LVEF) of at least 10 percentage points below the baseline measurement and to below 50% absolute value) or an asymptomatic decline in LVEF requiring treatment or leading to discontinuation of study treatment (non-serious adverse event of special interest)
- LVEF measurements over the course of the study; Incidence and severity of adverse events (AEs) and serious adverse events (SAEs)
- Incidence of laboratory test abnormalities.

Adverse events were graded by the investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.0.

The safety population for the APHINITY study comprised 4769 patients and was defined as all patients who received at least one dose of study medication (chemotherapy, pertuzumab/placebo, or trastuzumab).
The safety data are summarized according to the medication received:

- Study arm (Ptz+H+Chemo): 2364 patients who received at least one dose of pertuzumab. This includes 24 patients randomized to the comparator arm (Pla+H+Chemo) but who received at least one dose of pertuzumab.
- Comparator arm (Pla+H+Chemo): 2405 patients including 38 patients randomized to the Ptz+H+Chemo arm who did not receive pertuzumab.

In this application the safety data will be presented both for the initial trial period (CCOD 19 Dec 20216), where all AEs occurring during the study and until the end of treatment/treatment discontinuation visit 28 days after the last dose of study medication were collected (refer to Table 28) and for the post treatment period (CCOD 28 Nov 2024) where drug-related SAEs and AEs/SAEs qualifying for long-term reporting were collected.

The exposure to study treatment was balanced between the treatment arms, and most patients completed study treatment as planned. The overall safety profile of Ptz+H+Chemo in the APHINITY study was consistent with the known safety profile of pertuzumab in combination with trastuzumab and chemotherapy in HER2+ BC, and no new or unexpected toxicities were reported (19). In the post treatment period there were no new safety signals and nature and severity of AEs reported in the two treatment arms was consistent with the known safety profile of Ptz+H+Chemo and of Pla+H+Chemo (43). The overall safety profile of Ptz/Pla+H+Chemo in patients with node-positive disease was determined to be similar to that seen in the overall patient population.

Table 28 Overview of safety events in APHINITY, safety Evaluated Population. CCOD 19 Dec 2016 (19, 61, 63)

	Ptz+H+Chemo (N=2364)	Pla+H+Chemo (N=2405)	Difference, % (95 % CI)**
Number of adverse events, n	[redacted]	[redacted]	N/A
Number and proportion of patients with ≥1 adverse events, n (%)	[redacted](99.9%)	[redacted] (99.5%)	[redacted]
Number of serious adverse events*, n	1073	883	N/A
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	692 (29.3%)	585 (24.3%)	4.9 (2.4, 7.5)
Number of CTCAE grade ≥ 3 events, n	[redacted]	[redacted]	N/A
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	1518 (64.2%)	1379 (57.3%)	6.9 (4.1, 9.7)
Number of adverse reactions, n	[redacted]	[redacted]	N/A
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	[redacted]	[redacted]	[redacted]
Number and proportion of patients who had a dose reduction, n (%)	AEs that led to dose modification*** of Ptz: 723 patients (30.6%). AEs that led to dose modification*** of any study medication: 1217 patients (51.5%)	AEs that led to dose modification*** of placebo: 632 patients (26.3%). AEs that led to dose modification*** of any study medication: 1064 patients (44.2%).	4.3 (1.7, 6.9) 7.2 (4.4, 10.1)
Number and proportion of	370 patients (15.4%)	399 (16.6%)	-1.2 (-3,3, 0.9)

	Ptz+H+Chemo (N=2364)	Pla+H+Chemo (N=2405)	Difference, % (95 % CI)**
patients who discontinue treatment regardless of reason, n (%)			
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	AEs that led to withdrawal of Ptz: 166 patients (7.0%). AEs that led to withdrawal of any study medication: 309 patients (13.1%)	AEs that led to withdrawal of placebo: 139 patients (5.8%). AEs that led to withdrawal of any study medication: 277 patients (11.5%)	1.2 (-0.2, 2.7)

* 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).
** 95% CI for risk differences is calculated using the Wald method with continuity correction (Hauck-Anderson).
*** Dose reduction of pertuzumab was not permitted. The numbers in the table refer to dose modification, i.e. dose interruption or dose delay.
§ CTCAE v. 5.0 must be used if available. Applicant note: CTCAE v. 4.0 is used.
AE, adverse event; CI, confidence interval; Pla+H+Chemo, Placebo+Herceptin+Chemotherapy; Ptz+H+Chemo, Pertuzumab+Herceptin+Chemotherapy

Overview of safety - Primary CCOD (19 Dec 2016)

At the primary CCOD almost all patients in both treatment arms had experienced at least one AE. Consistent with the known safety profiles of the two treatment regimens, the most common AEs (≥ 30% in either treatment arm) were diarrhea (71.2% vs 45.2% in the Ptz+H+Chemo and Pla+H+Chemo arms, respectively), nausea (69.0% vs 65.5%), alopecia (66.7% vs 66.9%), fatigue (48.8% vs 44.3%), vomiting (32.5% vs 30.5%), arthralgia (28.7% vs 32.5%) and constipation (28.9% vs 31.6%). More than 90% of AEs in both treatment arms were Grade 1 or 2 in severity (61).

The proportion of patients who experienced at least one AE (any grade), fatal (Grade 5) AE starting during the treatment period, AE leading to withdrawal from targeted treatment, and AE leading to withdrawal from any study treatment [redacted] patients in the Ptz+H+Chemo arm experienced one or more Grade ≥3 AEs, SAEs, AEs leading to dose modification/interruption of any study treatment and AEs considered related to study treatment [redacted]

The most common (≥ 5%) Grade 3–5 AEs were neutropenia (385 [16.3%] vs 377 [15.7%)], febrile neutropenia (287 [12.1%] vs 266 [11.1%]), neutrophil count decreased (228 [9.6%] vs 230 [9.6%]), diarrhea (232 [9.8%] vs 90 [3.7%]) and anemia (163 [6.9%] vs 113 [4.7%]). Diarrhea was the only Grade ≥ 3 event that occurred with a ≥ 3% difference in incidence between treatment arms (19).

SAEs with a frequency of ≥ 5% are listed in Table 29 for the CCOD 19 Dec 2016. No SAEs had a frequency of ≥ 5% in the post-treatment period.

Table 29 Serious adverse events, APHINITY, Safety Evaluable Population (CCOD 19 Dec 2016) (19, 61, 63)

Adverse events	Ptz+H+Chemo (N=2364)		Pla+H+Chemo (N=2405)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Febrile neutropenia	208 (8.8%)	[redacted]	196 (8.1%)	[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).

Adverse Events to Monitor (EtMs) were prospectively defined based on the known safety profile of pertuzumab. The incidence of these events was consistent with the known safety profiles of both treatment regimens. Selected results are presented below:

Diarrhea

[redacted]

- Grade 3 - 4 diarrhea (preferred term [PT]) was most frequent during the targeted therapy + taxane chemotherapy treatment period [redacted] patients in the Ptz+H+Chemo arm vs. [redacted] of patients in the Pla+H+Chemo arm) compared to an incidence of [redacted] in the Ptz+H+Chemo arm and [redacted] in the Pla+H+Chemo arm during the post-chemotherapy targeted therapy period).
- The rate of treatment discontinuation of Perjeta/placebo due to diarrhea was [redacted] of patients in the Ptz+H+Chemo arm vs. [redacted] of patients in the Pla+H+Chemo). Discontinuation of any study treatment due to diarrhea occurred in [redacted] vs [redacted] of patients, respectively.

Rash

[redacted] More patients in the Ptz+H+Chemo arm experienced rash (51.9% vs 41.7%) (61). [redacted] with Grade 3-4 events reported in [redacted] in the Ptz+H+Chemo arm vs. [redacted] of patients in the Pla+H+Chemo arm [redacted]

- The most common PTs for rash were: rash (25.8% vs. 20.3%), erythema (9.9% vs. 8.9%), and Palmar-Plantar erythrodysaesthesia syndrome (9.2% vs. 6.6%) (61).

Leukopenia

[redacted] 1178 patients (49.8% in the Ptz+H+Chemo arm vs. 1158 patients (48.1%) in the Pla+H+Chemo arm) experienced at least one leukopenia AE (61) [redacted] Grade ≥ 3 events were reported in [redacted] in the Ptz+H+Chemo arm, and [redacted] in the Pla+H+Chemo arm [redacted]

- The most common reported event by PT were neutropenia (24.8% vs. 23.4%), febrile neutropenia (12.1% vs. 11.1%), and leukopenia (9.1% vs. 9.2%) (61).

Infusion-Related Reactions

- [redacted]Overall, infusion-related reactions (IRRs) were experienced in 1293 patients (54.7%) in the Ptz+H+Chemo arm and 1199 patients (51.3%) in the Pla+H+Chemo arm (61). Grade 1-2 IRRs were reported in[redacted]%) in the Ptz+H+Chemo arm vs [redacted]in the Pla+H+Chemo arm. Grade ≥3 events were reported in [redacted]in the Ptz+H+Chemo arm[redacted]in the Pla+H+Chemo arm;[redacted]
- The most common (≥5%) IRRs starting on the day of Perjeta/placebo infusion were fatigue (218 patients [9.2%] vs. 194 patients [8.3%], respectively), followed by arthralgia (182 patients [7.7%] vs. 213 patients [9.1%]), hot flush (157 patients [6.6%] vs. 148 patients [6.3%]), myalgia (120 patients [5.1%] vs. 144 patients [6.2%]), and dysgeusia (119 patients [5.0%] vs. 100 patients [4.3%]) (61).

Rash or similar skin adverse events; leukopenia and neutropenia, including febrile neutropenia, and infusion-related reactions were manageable and considered primarily related to chemotherapy. Diarrhea occurred more frequently in the Perjeta arm, and was among the main AEs leading to treatment withdrawal or dose modification. (61).

Cardiac Safety

Cardiovascular adverse events were reported according to pre-specified criteria (Common Terminology Criteria for Adverse events [NCI-CTCAE] and New York Heart Association [NYHA]). LVEF was assessed using either echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scans.

A primary cardiac event was defined as either “Heart Failure (NYHA Class III or IV) and a drop in LVEF of at least 10 EF points from baseline AND to below 50%” or “Cardiac Death”. A total of 25 patients met the criteria for a primary cardiac event:

- Heart failure (NYHA III or IV) with an LVEF decline was reported in 15 patients (0.6%) in the Ptz+H+Chemo arm vs 6 (0.2%). patients in the Pla+H+Chemo arm.
- Cardiac death (definite or probable) occurred in 2 patients (<0.1%) in each arm. One of these deaths (in the Pla+H+Chemo arm) was considered related to HER2-targeted treatment.

Most of the primary cardiac events were reported in patients who received anthracycline based treatment and all cardiac deaths occurred in patients who received anthracycline-based chemotherapy (19).

A secondary cardiac event was defined as an asymptomatic or mildly symptomatic (NYHA Class II) significant drop in LVEF defined as an absolute decrease of at least 10 EF points from baseline and to below 50%, confirmed by a second LVEF assessment within approximately three weeks of the first significant LVEF assessment or confirmed by the Cardiac Advisory Board. An event was only considered a secondary cardiac event if the patient did not experience a primary cardiac event during the study.

Secondary cardiac events occurred in 64 patients (2.7%) in the Ptz+H+Chemo arm and 67 patients (2.8%) in the Pla+H+Chemo arm (19)[redacted]

[redacted]

Other cardiac events were defined as acute coronary syndrome, acute myocardial infarction and severe rhythm disturbances requiring treatment. The incidence of any other cardiac event was similar in the Ptz+H+Chemo arm (2.7%) compared to the Pla+H+Chemo arm (2.4%) (61).

Post-treatment period (CCOD 28 Nov 2024)

Patient disposition during the follow-up period was comparable across both arms, with nearly all randomized patients entering the period (Ptz+H+Chemo: [redacted]%; Pla+H+Chemo: [redacted] Overall discontinuation rates were [redacted] (Ptz+H+Chemo) and [redacted] (Pla+H+Chemo). The primary reasons for discontinuation [redacted]: withdrawal by patient ([redacted] lost to follow-up ([redacted] and recurrence of disease [redacted].

During the post-treatment follow-up period, [redacted] experienced [redacted] in the Ptz+H+Chemo arm, and [redacted] experienced [redacted] events in the Pla+H+Chemo arm.

The most frequently reported AE during the post-treatment follow-up period was [redacted] in the Ptz+H+Chemo arm vs[redacted] [redacted] in the Pla+H+Chemo arm). All other AEs occurred [redacted] of patients in either treatment arm. [redacted] was experienced by [redacted] and [redacted] [redacted] in the Ptz+H+Chemo arm and Pla+H+Chemo arm, respectively (43).

Treatment-Related Serious Adverse Events and Death

Treatment-Related SAEs during post-treatment follow-up were [redacted] between groups, occurring in [redacted] in both the Ptz+H+Chemo arm ([redacted] events) and the Pla+H+Chemo arm ([redacted] events).

The most frequently reported system organ class for treatment-related SAEs was [redacted] [redacted] (Ptz+H+Chemo: [redacted] patients [[redacted] Pla+H+Chemo: [redacted] patients [[redacted]]) with [redacted] being the most often reported term by PT (Ptz+H+Chemo: [redacted] patients [[redacted] Pla+H+Chemo: [redacted] patients [[redacted] In the Ptz+H+Chemo arm, [redacted] treatment-related SAE ([redacted]) resulted in death. In the Pla+H+Chemo arm, [redacted] treatment-related SAEs ([redacted]resulted in the deaths of[redacted]

A total of [redacted] in the Ptz+H+Chemo arm and [redacted] in the Pla+H+Chemo arm had died during the study. The most common reason for death was [redacted]

Cardiac Safety

Analysis of cardiac events was based on data from randomization until the date of recurrence of disease or end of post-treatment follow-up, whichever occurs earlier.

At the final CCOD, a total [redacted] primary cardiac events were reported across the full study duration, reflecting an increase of [redacted] events since the primary data CCOD: 21 patients [redacted] in the Ptz+H+Chemo arm vs. [redacted] in the Pla+H+Chemo arm. The [redacted] primary events comprised the following:

- Heart Failure (New York Heart Association [NYHA] III or IV) with LVEF decline:
  - Ptz+H+Chemo arm: [redacted]
  - Pla+H+Chemo arm: [redacted]

- Cardiac Death (death with a definite or probable cardiac cause):
  - Ptz+H+Chemo arm: [redacted]
  - Pla+H+Chemo arm: [redacted]

Of the [redacted]atients who experienced a non-fatal primary cardiac event in the study, acute recovery (defined as two consecutive LVEF≥50%) was achieved as follows:

- [redacted]In the Ptz+H+Chemo arm, acute recovery was achieved in [redacted]
- In the Pla+H+Chemo arm, acute recovery was achieved in [redacted]

A total [redacted] patients had a secondary cardiac event reported: [redacted] in the Ptz+H+Chemo arm ([redacted] and [redacted] in the Pla+H+Chemo arm [redacted]). Of the [redacted] patients, LVEF recovery was achieved [redacted] in the Ptz+H+Chemo arm vs [redacted] in the Pla+H+Chemo arm. The median time to LVEF recovery [redacted] in the Ptz+H+Chemo arm vs [redacted] in the Pla+H+Chemo arm (43).

Adverse events in the health economic model

AEs are included in the model if meeting all the following conditions:

1. Severe
2. CTAE (Common Terminology Criteria for Adverse Events) >= 3
3. Treatment related
4. In node positive population
5. Occurring during treatment and post treatment periods

In the model, all treatment-related adverse events defined above have been included. The number of occurrences and their standard deviations (SDs) for each of the population are included in the “Adverse Events” sheet. The frequencies (occurrences) were obtained from the APHINITY trial.

Adverse event costs are calculated and applied in one time approach. So adverse events occur only in the first model cycle as a one-time cost. Disutilities associated with adverse events are not considered. They are assumed to be considered along with the health state utilities.

Table 30 Adverse events used in the health economic model

Adverse event	Intervention - % of patients	Comparator - % of patients	Source
[redacted]	[redacted]	[redacted]	APHINITY (Node positive population)
[redacted]	[redacted]	[redacted]	APHINITY (Node positive population)
[redacted]	[redacted]	[redacted]	APHINITY (Node positive population)
[redacted]	[redacted]	[redacted]	APHINITY (Node positive population)
[redacted]	[redacted]	[redacted]	APHINITY (Node positive population)
[redacted]	[redacted]	[redacted]	APHINITY (Node positive population)
[redacted]	[redacted]	[redacted]	APHINITY (Node positive population)
[redacted]	[redacted]	[redacted]	APHINITY (Node positive population)
[redacted]	[redacted]	[redacted]	APHINITY (Node positive population)
[redacted]	[redacted]	[redacted]	APHINITY (Node positive population)

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

N/A

Table 31 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								

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

Table 32 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-3L	APHINITY (BO25126)	Clinical effectiveness and utility. Section 10.1.
EORTC QLQ-C30	APHINITY (BO25126)	Clinical effectiveness. See Appendix F.

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-3L, European Quality of Life 5-Dimension 3-Level Questionnaire

Secondary efficacy objectives in APHINITY included the evaluation of the treatment effect of Ptz+H+Chemo compared to Pla+H+Chemo based on patient-reported outcome (PRO) instruments (see all PROs included in the study in Appendix A). HRQoL assessed using the EuroQol-5 Dimensions-3 Levels Questionnaire (EQ-5D-3L) and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) will be presented in this application

10.1 Presentation of the health-related quality of life measured by EQ-5D-3L

10.1.1 Study design and measuring instrument

The APHINITY study design is described in section 6.1.1. Secondary objectives included evaluating HRQoL using the EQ-5D-3L instrument in the Ptz+H+Chemo and Pla+H+Chemo groups, to support pharmacoeconomic modeling. HRQoL was assessed in the APHINITY trial using the EQ-5D-3L instrument, in accordance with EMA guidance and international trial standards applicable at the time of study initiation (2011). The EQ-5D-5L instrument had not yet been developed when the trial protocol was finalized.

The EQ-5D-3L is a validated, descriptive self-reported health status questionnaire designed to generate health utility scores for use in health economic analyses. It consists of five dimensions assessing mobility, self-care, usual activities, pain/discomfort, and anxiety/depression where dimension has 3 levels: No problems, some problems, and extreme problems. Patients are requested to indicate their health status by selecting the most appropriate statement within each of the five dimensions. This selection yields a single-digit number for each dimension, which represents the chosen health level. These five single-digit numbers can then be combined to form a five-digit number that represents the participant's overall health state. Data collection

Data collection

Assessments of the EQ-5D-3L utility index were conducted at baseline; “Week 13”, Week 25; treatment completion; and during post-treatment follow-up at 18, 24 and 36 months. The time point denoted as “Week 13” corresponds to the end of taxane treatment in all patients, the actual time of this assessment depends on the type of chemotherapy. For patients receiving anthracycline-based chemotherapy, the actual time point was Week 10 or Week 13 of HER2-targeted treatment (depending on the chemotherapy regimen given). For patients receiving non-anthracycline-based chemotherapy (i.e., the Ptz+TCH regimen), this was Week 19 of HER2-targeted treatment.

Data was collected in the ITT population and patients were required to complete the PRO measures until recurrence or until 36 months after randomization, regardless of whether the patient completed study treatment or not.

Patients completed the questionnaires at the center prior to physician assessment and prior to receiving study treatment. It was recommended that a key person (e.g., research nurse) at each center be responsible for questionnaire data collection to optimize compliance and completeness of the data.

The completion rates for the EQ-5D 3L questionnaire were consistently high throughout the study with a completion rate >85% throughout the study. Completion rates were comparable across treatment arms and between anthracycline/non-anthracycline chemotherapies (57). Therefore, completion rates and results are reported for all patients.

Table 33 Pattern of missing data and completion, EQ-5D-3L, ITT population. CCOD: 19 Dec 2016 (63).

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients “at risk” at time point X	Number of patients who completed (% of patients expected to complete)
Ptz+H+Chemo				
Baseline	2400	[redacted]	[redacted]	[redacted]
Week 13*	2400	[redacted]	[redacted]	[redacted]
Week 25	2400	[redacted]	[redacted]	[redacted]
End of treatment (Month 12)	2400	[redacted]	[redacted]	[redacted]
Follow-up: Month 18	2400	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Follow-up: Month 24	2400	[redacted]	[redacted]	[redacted]
Follow-up: Month 36	2400	[redacted]	[redacted]	[redacted]
		Pla+H+Chemo		
Baseline	2404	[redacted]	[redacted]	[redacted]
Week 13*	2404	[redacted]	[redacted]	[redacted]
Week 25	2404	[redacted]	[redacted]	[redacted]
End of treatment (Month 12)	2404	[redacted]	[redacted]	[redacted]
Follow-up: Month 18	2404	[redacted]	[redacted]	[redacted]
Follow-up: Month 24	2404	[redacted]	[redacted]	[redacted]
Follow-up: Month 36	2404	[redacted]	[redacted]	[redacted]

*The time point "Week 13" in this table and the associated programmed outputs corresponds to the end of taxane treatment; the actual time depends on the type of chemotherapy received. For patients receiving non-anthracycline-based chemotherapy (i.e., the Ptz+TCH regimen), this was Week 19 of HER2-targeted treatment.

10.1.2 HRQoL results

EQ-5D-3L health states from APHINITY have been converted to the Danish population using Danish preference weights for EQ-5D-3L (72) (73).

[redacted]

Table 34 HRQoL, EQ-5D-3L utility index scores in APHINITY, ITT population. CCOD: 19 Dec 2016

	Intervention Ptz+H+Chemo		Comparator Pla+H+Chemo		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 13*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment (Month 12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up: Month 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up: Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up: Month 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 13 Mean change from baseline in EQ−5D−3L Utility Scores, ITT population CCOD: 19 Dec 2016.

CI, confidence interval; EQ-5D-3L, European Quality of Life 5-Dimension 3-Level Questionnaire; Fup, Follow-up period

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

10.2.1 HSUV calculation

Clinical description of disease specific and generic health-related quality of life (HRQoL), setting and measures in the APHINITY trial are described in the clinical part of this document.

The EQ-5D-3L summary scores were collected at baseline, during treatment, and post-treatment as long as the patient was disease-free (last assessment 3 years post randomization). The questionnaire was administered before any other study procedure was performed during the study visit.

Utilities by state were estimated through a linear mixed effects model on post-baseline utilities while controlling for centralized baseline utilities and health state using random intercepts for each patient. Patients needed to have baseline utilities and observations with undefined health state are dropped from the analysis.

No imputation was done to account for missing data and da without completeness was discarded. [redacted], the assessment was that bias in reported QoL was not of big impact. Additionally, while we do not have the relevant data for EQ5D, Table 59 in the dossier reports that administrative [redacted] Although it cannot be finally verified, given that the data is not

available, [redacted].

We adjust the development of utility values (health state utility values, HSUVs) for patients' increasing age according to DMC Aldersjustering for sundheds-relateret livskvalitet document. Model also allows data from Ara & Brazier (74).

10.2.1.1 Mapping

The original EQ-5D-3L data from APHINITY trial was mapped to a 5L value set using the reverse crosswalk method by van Hout et al (2021) (73) and implemented using eq5d R package (fragla/eq5d - GitHub, accessed November 5, 2025, https://github.com/fragla/eq5d). The van Hout (2021) model represents the current state-of-the-art for mapping 3L descriptive responses to 5L value sets. The eq5d package provides a transparent, validated, and robust implementation of this exact methodology. A similar procedure has been used in our earlier submissions to DMC.

10.2.2 Disutility calculation

Utility estimates are derived from the APHINITY trial and from the literature regarding periods and health states beyond the trial. Therefore, AE specific disutilities are not explicitly considered to avoid double counting in the model.

10.2.3 HSUV results

In the base case analysis, the pooled node positive EQ-5D utility values from APHINITY and the utility values form Lloyd et al. (7) are used to model quality of life of the patients Table 35. Alternatives data sources are explored in sensitivity analyses (see section 5.2).

Table 35 Overview of health state utility values [and disutilities]

	Results [SE]	Instrument	Tariff (value set) used	Comments
HSUVs				
IDFS - On chemotherapy	[redacted]	EQ-5D-5L	DK	Estimate is based on mean of both APHINITY trial arms.
IDFS - On treatment / off chemotherapy	[redacted]	EQ-5D-5L	DK	Estimate is based on mean of both APHINITY trial arms.
IDFS - Off treatment	[redacted]	EQ-5D-5L	DK	Estimate is based on mean of both APHINITY trial arms.

	Results [SE]	Instrument	Tariff (value set) used	Comments
Locoregional recurrence	[redacted]	EQ-5D-5L	DK	Estimate is based on mean of both APHINITY trial arms.
Remission	[redacted]	EQ-5D-5L	DK	Estimate is based on mean of both APHINITY trial arms.
1st line metastatic	0.773 [NA]	EQ-5D-3L	UK	Base-case estimate is based on literature - Lloyd et al. (7) No variation in PSA, no SE available.
	0.650 [0.294]			Estimate is based on literature - Hedden et al (75)
	0.685 [0.113]			Estimate is based on literature - Lidgren et al. (76)
	0.806 [0.007]			Estimate is based on literature - Paracha et al. (77)
2nd line+ metastatic	0.520	EQ-5D-3L	UK	Base-case estimate is based on literature - Lloyd et al. (7) No variation in PSA, no SE available.
	0.290 [0.245]			Estimate is based on literature - Hedden et al. (75)
	0.685 [0.113]			Estimate is based on literature - Lidgren et al. (76)
	0.536 [0.076]			Estimate is based on literature - Paracha et al. (77)
Death	0			Assumption

EQ-5D-3L, European Quality of Life 5-Dimension 3-Level Questionnaire EQ-5D-5L, European Quality of Life 5-Dimension 5-Level Questionnaire; IDFS, Invasive Disease-Free survival; PSA, Probabilistic Sensitivity Analysis; SE, Standard Error

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

External utility values are applied in 1L and 2L metastatic disease. In our base we use Lloyd et al. The study was a cross-sectional preference valuation study conducted in the United Kingdom. Objective of the study was to obtain societal preference values (utilities) for various stages of metastatic breast cancer and common chemotherapy-related toxicities. The study utilized Standard Gamble interviews, which is a technique used to measure health state preferences by determining the maximum risk of death an individual is willing to accept to avoid a specific health state. A mixed model analysis was

used to determine the utility scores for different combinations of disease states and toxicities.

Inclusion Criteria were the following:

- Population: Members of the general public.
- Geography: Residents of the United Kingdom, specifically recruited from Greater London.
- Gender: Equal proportions of men and women were recruited. Consent: All participants were required to provide written informed consent.

Exclusion Criteria were the following:

- Lack of Understanding: Participants were excluded if, in the interviewer's opinion, they failed to understand the complex Standard Gamble task (6 participants were excluded for this reason).
- Impaired Mobility (Practical): Because participants had to attend interviews in person at the UBC offices, those with severely compromised mobility were effectively excluded from participating.

10.3.1 Study design

See above

10.3.2 Data collection

Data collection involved structured, face-to-face interviews with 100 participants. Initial Assessment: Participants completed a sociodemographic questionnaire and the EQ-5D instrument to record their own current health status. Visual Analogue Scale (VAS): Participants first rated various health state descriptions (including "dead" and "full health") on a "feeling thermometer" ranging from 0 to 100. Standard Gamble Task: For each health state, participants were asked to choose between living in a hypothetical health state for 10 years or taking a gamble with varying probabilities of "full health" versus "worst health" (or "dead"). Health States Rated: Each participant reviewed a total of 10 health states, including anchor states (stable, responding, and progressive disease) and a subset of combinations involving toxicities like hair loss, fatigue, or febrile neutropenia.

10.3.3 HRQoL Results

N/R see 10.2.3

10.3.4 HSUV and disutility results

N/R see 10.2.3

Table 36 Overview of health state utility values [and disutilities]

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

Table 37 Overview of literature-based health state utility values

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

11. Resource use and associated costs

11.1 Medicines - intervention and comparator

Costs and resource use vary depending on the administered treatment and health states. The model includes drug costs, administration costs, subsequent therapy costs, disease management costs, and AE costs. The costs included are consistent with the limited societal perspective as described in the DMC guidelines (78). Drug costs are estimated from Medicinpriser.dk, where administration costs, disease management costs, and AE costs are based on the Danish diagnose relative group (DRG) tariffs 2025. Treatment durations are described in Section 8.3.

For all pharmaceuticals administered in the model, pharmacy purchase prices have been used. Drug acquisition costs are applied to patients in each health state. For intravenous therapies, the cost-effectiveness analysis assumes no vial sharing, and uses the cheapest vial size per mg.

Medicines used in the intervention and comparator groups in the model are described in Table 38. There were two main chemotherapy regimens allowed in APHINITY trial. Patients used either anthracycline-based regimens or non-anthracycline regimen based on the locally standard HER2+ adjuvant regimen chosen by investigator.

Table 38 Medicines used in the model

Medicine	Dose	Relative dose intensity (assumed in base case)	Frequency	Vial sharing
PHESGO	10	100%	Every 3 weeks	SC injection
PHESGO	15	100%	Every 3 weeks	SC injection
Herceptin	150	100%	Every 3 weeks	Yes

Medicine	Dose	Relative dose intensity (assumed in base case)	Frequency	Vial sharing
Herceptin	150	100%	Every 3 weeks	Yes
Trastuzumab biosimilar	150	100%	Every 3 weeks	Yes
Trastuzumab biosimilar	150	100%	Every 3 weeks	Yes
Docetaxel	20	100%	Every 3 weeks	Yes
Docetaxel	80	100%	Every 3 weeks	Yes
Paclitaxel	30	100%	Every 3 weeks	Yes
Paclitaxel	100	100%	Every 3 weeks	Yes
Doxorubicin	10	100%	Every 3 weeks	Yes
Doxorubicin	50	100%	Every 3 weeks	Yes
Epirubicin	10	100%	Every 3 weeks	Yes
Epirubicin	50	100%	Every 3 weeks	Yes
Cyclophosphamide	500	100%	Every 3 weeks	Yes
Cyclophosphamide	1 000	100%	Every 3 weeks	Yes
5-Fluorouracil	2 500	100%	Every 3 weeks	Yes
5- Fluorouracil	5 000	100%	Every 3 weeks	Yes
Carboplatin	150	100%	Every 3 weeks	Yes
Carboplatin	450	100%	Every 3 weeks	Yes

11.2 Medicines– co-administration

N/A

11.3 Administration costs

We assume that all infusion treatment alternatives have the same fixed administration cost in all cycles. The administration cost of 2136 DKK (DRG 2025, 17MA98) in the first cycle and in the subsequent cycles. The drug administration costs in the model are based on the DRG tariffs for 2025, which account for the complexity of the administration mode (Table 39).

- Intravenous (IV) administration costs utilise the standard DRG tariffs.
- Subcutaneous (SC) administration cost is calculated separately:
    - The total estimated cost for eight SC injections (based on Atezolizumab every three weeks) was DKK 14,315, including time for the doctor, nurse, bio-analytics, patient costs, policlinic assessment, and facility fees (per the DMC resource use document ”Medicinrådets tværgående omkostningsanalyse vedr. PD-(L)1-hæmmere. Gælder for subkutan og intravenøs behandling; version 1.1, tabel 7”)(79).
    - To specifically model the SC administration cost, only the nurse time and facility fees (DKK 1,634) were used and divided by eight injections, resulting in a cost of DKK 204.25 per SC administration.

Table 39 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
IV infusion	Every 3rd week	2136 DKK	17MA98	DRG 2025
Subcutaneous infusion	Every 3rd week	204.25 DKK	N/A	Medicinrådets tværgående omkostningsanalyse vedr. PD-(L)1-hæmmere. Gælder for subkutan og intravenøs behandling; version 1.1, table 7 (79)
Oral	-	0	-	-

11.4 Disease management costs

In each cycle that a patient remained alive, supportive care costs were implemented and varied between the IDFS, non-metastatic recurrence, remission, 1st line mBC and subsequent treatment lines mBC health states, regardless of the treatment arm utilised. These costs are indicative of healthcare resource consumption that is specific to the disease status, rather than the treatment arm employed.

Supportive care costs are applied in every cycle a patient remains alive. These costs are independent of the treatment arm used but vary based on the patient's current health state. Specifically, costs differ between the IDFS, non-metastatic recurrence, remission, 1st line mBC, and subsequent treatment lines mBC health states, reflecting healthcare resource consumption tied to the disease status itself.

Resource usage of the following items were applied per health state if applicable:

Oncologist assessment
Mammogram
ECHO/MUGA scan
CT scan

Resource use in IDFS state on treatment

Patients who are in IDFS state for the first two years are assumed to have four visits with an oncologist (every 3 months) and require completing a mammogram, an ECHO/MUGA scan and a CT scan once per year.

Resource use in IDFS state off treatment

In the following 3-5 years, patients who remain in IDFS and are off treatment instead have 2 annual visits with an oncologist and once per year undergo a mammogram, an ECHO/MUGA scan and a CT scan.

Resource use in Remisison state

The remission state is the least resource-intensive, requiring just one annual visit with an oncologist and one mammogram.

Resource use in Non metastatic recurrence state

For this state, resource usage includes four oncologist assessments, one mammogram, two ECHO/MUGA scans, and two CT scans annually.

1st line metastatic state

Resource utilisation is categorised into early and late relapsers following 1st line treatment. To simplify, the same frequency of resource use is assumed, considering the increased follow-up needs in the metastatic setting. Frequency inputs can be adjusted in the model's Supportive Care tab.

The required resources for patients with an early and late recurrence after undergoing treatments are six oncologist assessments, two ECHO/MUGA scans, and four CT scans each year.

2nd line + metastatic state

Resource utilisation is categorised into early and late relapsers after 2nd line+ treatments. To simplify, the same frequency is applied, considering the increased follow-up needs in the metastatic setting. Frequency inputs can be adjusted in the model's Supportive Care tab.

Early disease recurrence

Patient have six oncologist assessments, four CT scans, and three ECHO/MUGA scans annually.

Late disease recurrence

Late relapses, like early disease relapses, require six oncologist assessments, four CT scans, but less ECHO/MUGA scans, assumed two each year.

Table 40 Disease management costs used in the model (annual)

Activity	Frequency *IDFS on treatment*	Frequency IDFS off treatment	Frequency remission	Frequency non-metastatic recurrence	Frequency. *1st line metastatic (early and late relapse)*	Frequency 2nd *line metastatic (early relapse)*	Frequency 2nd line metastatic (late relapse)	Unit cost [DKK]	DRG code	Ref.
Oncologist (visit)	4	2	1	4	6	6	6	1 578	N/A	Cost of chief physician according to the DMC "Værdisætning af enhedsomkostninger" v1.8
Mammogram	1	1	1	1	0	0	0	4 512	36PZ10	DK-DRG
ECHO **MUGA scan**	1	1	0	2	2	3	2	2 111	05PR04 17MA98	DK-DRG
CT scan	1	1	0	2	4	4	4	2 401	36PR07	DK-DRG

11.5 Costs associated with management of adverse events

Adverse event costs are calculated and applied in one time approach as described in Section 9. So adverse events occur only in the first model cycle as a one-time cost. Disutilities associated with adverse events are not considered.

Table 41 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
Cardiac failure	DRG 2020, 05MA08	40 702 DKK
Anaemia	DRG 2025, 16MA98	1 578 DKK
Diarrhoea	DRG 2025, 06MA11	1 578 DKK
Ejection fraction decreased	DRG 2025, 16MA98	1 578 DKK
Fatigue	DRG 2025, 16MA98	1 578 DKK
Febrile neutropenia	DRG 2025, 16MA03	1 578 DKK
Leukopenia	DRG 2025, 16MA98	1 578 DKK
Neutrophil count decreased	DRG 2025, 16MA98	1 578 DKK
White blood cell count decreased	DRG 2025, 16MA98	1 578 DKK

11.6 Subsequent treatment costs

Subsequent treatment cost in the model contains disease management cost and supportive care costs, which contain drug costs and cost related to healthcare resource utilisation. Medicines used are reported in Table 42. Monthly costs (used for model calculation) classified to drug costs, other healthcare costs and total costs (drug + healthcare utilisation) are reported in Table 43.

Table 42 Medicines of subsequent treatments

Medicine	Share (%)	Dose	Relative dose intensity	Frequency	Vial sharing
Non-metastatic recurrence					
Herceptin IV (a) + docetaxel (b)	5%	(a) Initial dose 8 mg/kg, 6mg/kg every 3 weeks thereafter (b): 100 mg/m2 every 3 weeks	100%	18 cycles	Yes

Medicine	Share (%)	Dose	Relative dose intensity	Frequency	Vial sharing
Herceptin SC (a) + docetaxel (b)	95%	(a) 600mg Q3W (b): 100 mg/m2 Q3W	100%	18 cycles	No
Metastatic 1st line (early disease recurrence)					
Herceptin IV (a) + docetaxel (b)	10	(a) Initial dose 8 mg/kg, 6mg/kg Q3W thereafter (b): 100 mg/m2 Q3W	100%	18 cycles	Yes
Herceptin SC + docetaxel	24	(a) 600 every 3 weeks (b): 100 mg/m2 Q3W	100%	18 cycles	No
Trastuzumab deruxtecan	66	5,4 mg/kg Q3W	100%	54.8 cycles	Yes
Metastatic 1st line (late disease recurrence) - PHT arm					
Phesgo	71.2	1200mg/600mg initial cycle followed by 600mg/600mg Q3W	100%	37.4 cycles	Yes
Trastuzumab bx+ docetaxel	22.9	(a) 600 mg Q3W (b): 100 mg/m2 Q3W	100%	23.7 cycles	Yes
Docetaxel	5.9	(b): 100 mg/m2 Q3W	100%	6 cycles	Yes
Metastatic 1st line (late disease recurrence) - HT arm					
Phesgo	71.2	1200mg/600mg initial cycle followed by 600mg/600mg Q3W	100%	37.4 cycles	Yes
Trastuzumab (a)+ docetaxel (b)	22.9	(a) 600 mg Q3W (b): 100 mg/m2 Q3W	100%	23.7 cycles	Yes

Medicine	Share (%)	Dose	Relative dose intensity	Frequency	Vial sharing
Docetaxel	5.9	100 mg/m2 Q3W	100%	6 cycles	Yes
Metastatic 2nd line+ (early disease recurrence)					
Kadcyla	67	3.6 mg/kg Q3W	100%	19.3 cycles	Yes
Herceptin IV (a) + capecitabine (b)	5	(a) Initial dose 8 mg/kg, 6mg/kg Q3W thereafter (b) 2000 mg/kg pr day	100%	9.4 cycles	Yes
Herceptin SC (a) + capecitabine (b)	11	(a) 600 mg Q3W (b) 2000 mg/m2 pr day	100%	9.4 cycles	Yes
Capecitabine	17	2000 mg/m2 pr day	100%	6 cycles	Yes
Metastatic 2nd line+ (late disease recurrence)					
Trastuzumab bx + capecitabine	20	(a) Initial dose 8 mg/kg, 6mg/kg Q3W thereafter (b) 2000 mg/m2 pr day	100%	54.8 cycles 6 cycles	Yes
Trastuzumab deruxtecan	80	5,4 mg/kg Q3W	100%	54.8 cycles	Yes

Table 43 Monthly cost (used for model calculation)

Health state	Drug costs (DKK)	Follow-up (healthcare utilisation excl. drugs) cost (DKK)	Total costs
IDFS - Year 1 & 2	0.00	1 278.00	1 278
IDFS - Year 3 - 5	0.00	1 015.00	1 015
IDFS - Subsequent years	0.00	0.00	0
Remission	0.00	507.50	508
Non-metastatic recurrence	15 074.69	1 654.00	16 729

Health state	Drug costs (DKK)	Follow-up (healthcare utilisation excl. drugs) cost (DKK)	Total costs
Metastatic 1st line (early disease recurrence)	43 220.52	1 941.17	45 162
Metastatic 1st line (late disease recurrence) -PHT arm	34 659.88	1 941.17	36 601
Metastatic 1st line (late disease recurrence) - HT arm	34 659.88	1 941.17	36 601
Metastatic 2nd line+ (early disease recurrence)	27 746.81	2 117.08	29 864
Metastatic 2nd line+ (late disease recurrence)	52 289.80	1 941.17	54 231

IDFS, Invasive Disease-Free survival; HT, trastruzumab+chemo; PHT, Perjeta+Herceptin+Chemo

11.7 Patient costs

Patient transportation costs are included in the model according to the DMC method guidelines (ref). The unit cost per patient hour was estimated to be 188 DKK and the transportation cost was estimated to be 3.79 DKK per km with the assumption of an average distance to the hospital of 40 km (roundtrip) in line with the DMC guidelines.

We estimated the duration of time that patients spend undergoing specific medical follow-ups:

- 45 min for an assessment by oncologist
- 30 min mammogram scan
- 60 min ECHO/MUGA scan
- 30 min CT scan

Using these time estimates and the frequency of each type of visit during a given health state, we calculated the total amount of time a patient spends undergoing medical follow-ups per cycle in the "Supportive Care" tab of the model. Based on these calculations, we then determined the frequency of travel per cycle required for these visits and used this information in the "Cost Input" tab to calculate the total time spent on informal care for each health state.

Table 44 Patient costs used in the model

Activity	Units; Unit costs (DKK)	Source
Activity	188	DMC method guidelines

Activity	Units; Unit costs (DKK)	Source
Transport cost per visit	20 km per visit 3.79 DKK per km	DMC method guidelines
Travel frequency per health state per model cycle		
IDFS on treatment	0.33	Assumption on frequency of resource use (see chapter 11.4)
IDFS off treatment	0	Assumption on frequency of resource use (see chapter 11.4)
Non-metastatic recurrence	0.33	Assumption on frequency of resource use (see chapter 11.4)
Remission	0	Assumption on frequency of resource use (see chapter 11.4)
1st line metastatic (early recurrence)	0.50	Assumption on frequency of resource use (see chapter 11.4)
2nd line metastatic (early recurrence)	0.50	Assumption on frequency of resource use (see chapter 11.4)
1st line metastatic (late recurrence)	0.50	Assumption on frequency of resource use (see chapter 11.4)
2nd line metastatic (late recurrence)	0.50	Assumption on frequency of resource use (see chapter 11.4)
Time spent on informal care per model cycle (hours)		
IDFS on treatment	2.58	Assumptions on frequency and length of medical visits (see chapter 11.4 and 0)
IDFS off treatment	0.00	Assumptions on frequency and length of medical visits (see chapter 11.4 and 0)
Non-metastatic recurrence	2.70	Assumptions on frequency and length of medical visits (see chapter 11.4 and 0)
Remission	0.00	Assumptions on frequency and length of medical visits (see chapter 11.4 and 0)
1st line metastatic (early recurrence)	2.87	Assumptions on frequency and length of medical visits (see chapter 11.4 and 0)

Activity	Units; Unit costs (DKK)	Source
2nd line metastatic (early recurrence)	2.49	Assumptions on frequency and length of medical visits (see chapter 11.4 and 0)
1st line metastatic (late recurrence)	2.87	Assumptions on frequency and length of medical visits (see chapter 11.4 and 0)
2nd line metastatic (late recurrence)	2.87	Assumptions on frequency and length of medical visits (see chapter 11.4 and 0)

IDFS, Invasive Disease-Free survival

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

N/A

12. Results

12.1 Base case overview

An overview of the base case is described in Table 45.

Table 45 Base case overview

Feature	Description
Comparator	Trastuzumab + placebo IV
Type of model	Semi-Markov state transition model
Time horizon	52 years (life time)
Treatment line	Adjuvant.
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-3L in study APHINITY (63). Danish population weights were used to estimate health-state utility values (72) and mapped to EQ-5D-5L using reverse cross walk (73)
Costs included	Medicine costs Hospital costs Procedure costs Costs of adverse events Patient costs

Feature	Description
Dosage of medicine	According to SmPC taken into account weight
Average time on treatment	Phesgo: 11.13 months trastuzumab + placebo IV: 11.25 months
Parametric function for PFS	Phesgo: KM + Gompertz tail for IDFS trastuzumab + placebo IV: KM + Gompertz tail IDFS
Parametric function for OS	Phesgo: Exponential trastuzumab + placebo IV: Exponential
Inclusion of waste	No, vial sharing is assumed
Average time in model health state	Intervention vs comparator
In IDFS	17.50 vs. 16.35 years
In non-meta. rec.	0.03 vs. 0.04 years
In remission	0.226 vs. 0.32 years
In metastatic	0.25 vs. 0.33 years
In metastatic prog.	0.37 vs. 0.53 years
Death	N/A

IDFS, Invasive Disease-Free survival; KM, Kaplan-Meier; OS, Overall survival; PFS, Progression-Free survival

12.1.1 Base case results

Table 46 shows base case results for Phesgo vs trastuzumab + placebo IV using the assumptions presented in 32. The mean treatment acquisition cost for Phesgo was [redacted] DKK. The mean total cost including cost of drug administration, adverse event management, supportive, post progression treatments and patient costs was [redacted] for the Phesgo compared to [redacted] for the trastuzumab + placebo IV. The mean total incremental cost was therefore [redacted] DKK.

In terms of health outcomes, Phesgo vs trastuzumab + placebo IV combinations generated 18.003 and 17.492 mean life years respectively, resulting in 0.511 mean life years gained in favour of Phesgo. In terms of mean QALYs, Phesgo generated 14.792 QALYs in total, while the trastuzumab + placebo IV combination generated 14.323 QALYs, resulting in a mean QALY gain of 0.470 in favour of Phesgo.

Base case cost-effectiveness results show a mean cost per life year gained of [redacted] DKK and a mean cost per QALY gained (ICER) of [redacted] DKK at the proposed list price for Phesgo.

Table 46 Base case results, discounted estimates

	Phesgo	trastuzumab + placebo IV	Difference
Medicine costs	[redacted]	[redacted]	[redacted]
Medicine costs – co-administration	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
Disease management costs			
Costs associated with management of adverse events	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]
Patient costs	[redacted]	[redacted]	[redacted]
Palliative care costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Life years gained - In IDFS	17,182	16,318	0,864
Lige years gained - In non-meta. rec.	0.03	0.04	-0.01
Life years gained - In remission	0.21	0.31	-0.09
Life years gained - In metastatic	0.23	0.32	-0.09
Life years gained - In metastatic prog.	0.35	0.51	-0.16
Life years gained - Death	0.00	0.00	0.00
Total life years	**18.003**	**17.492**	**0.511**
QALYs gained - In IDFS	14.227	13.518	0.710
QALYs gained - In non-meta. rec.	0.02	0.03	-0.01
QALYs gained - In remission	0.18	0.26	-0.08
QALYs gained - In metastatic	0.18	0.25	-0.07
QALYs gained - In metastatic prog.	0.18	0.26	-0.08
QALYs gained - Death	0.00	0.00	0.00
QALYs (adverse reactions)	0.00	0.00	0.00

	Phesgo	trastuzumab + placebo IV	Difference
Total QALYs	**14.792**	**14.323**	**0.470**
Incremental costs per life year gained		[redacted]	
Incremental cost per QALY gained (ICER)		[redacted]	

ICER, Incremental Cost-Effectiveness Ratio; IDFS, Invasive Disease-Free survival; QALY, Quality-Adjusted Life-Year

12.2 Sensitivity analyses

12.2.1 Assessment on uncertainty

The model presents the cost-effectiveness analysis of Phesgo for the adjuvant treatment of patients with breast cancer. The economic evaluation is informed by the phase III randomised clinical trial comparing Phesgo vs. trastuzumab + placebo IV. The phase III head-to-head trial (APHINITY) produced statistically and clinically meaningful results.

The model adopts a semi-Markov model approach, combining results from the APHINITY trial regarding IDFS and results from other trials concerning disease stages following the IDFS state. Transitions related to the metastatic states are derived from other trials by fitting exponential survival functions to the data. This is a straightforward approach that avoids making the model overly complicated. Although there is some uncertainty associated with this part of the model, cost-effectiveness is primarily determined by over 10 years of follow-up in the APHINITY trial. Moreover, model based of APHINITY and related assumptions have already been subject to HTA in many countries. It is unlikely that structural or modelling uncertainty would significantly influence decision uncertainty. Therefore, we do not explore structural or modelling uncertainty in further detail.

There is some temporal uncertainty related to modelling. Because of the nature of early breast cancer, the number of recurrence events during the study's follow-up period was limited, and secondly, treatment options have advanced since the study was initiated. Therefore, it can be expected that survival following metastatic progression would be better today than what the APHINITY study indicates. Therefore, the model applied data from other trials to inform a plausible trajectory of the disease.

Typically, potentially significant uncertainty is related to utilities. Even though we used reliable trial data, we explored how different utility measures may affect the results and decision uncertainty. Since data were not collected with the EQ-5D instrument beyond the first three years in the APHINITY study, baseline data regarding utilities for disease progression to metastases had to be obtained from literature. There is variation in these utility estimates, but the impact on the results (for instance on the Incremental Cost-Effectiveness Ratio [ICER]) is marginal.
Only the most relevant adverse events were included in the model, although the model allows incorporation of all adverse events reported in the APHINITY trial. However,

adverse events have only a marginal impact on the results; therefore, the associated decision or modelling uncertainty is not considered meaningful and is not explored.

Along with utilities, one typical source of uncertainty is related to survival extrapolation. We applied a KM + parametric tail approach, as it fits the observed data more closely than a fully parametric model. It can be argued, however, that the KM + parametric tail approach lacks a coherent statistical framework, makes uncertainty quantification (particularly in PSA) difficult, and may introduce discontinuities or arbitrary choices at the splice point. Nevertheless, as we show in the sensitivity analysis, the fully parametric approach produces very consistent results with KM + parametric tail.

The uncertainty described above is explored in the sensitivity analysis. We apply deterministic (DSA) and probabilistic (PSA) sensitivity analysis, and scenario analyses are conducted to assess the robustness of the base case assumptions and parameter uncertainty. For the DSA / univariate sensitivity analysis, the calculation of the lower and upper parameter values is by default based on the parameter distribution from the PSA or assuming standard error of 0.20 more normal-like or mildly skewed variable distribution or 0.25 for potentially more skewed or wider variable distribution. Both can be changed in the model (see e.g. Sensitivity Chart and Cost Inputs sheets).

12.2.2 Deterministic sensitivity analyses

Deterministic sensitivity analyses were performed on key cost-effectiveness parameters from parameter uncertainty point of view. All outcomes are half-cycle corrected and discounted. Table 47-Table 48 and Figure 14 show the results of the sensitivity analyses in relation to the base case ICER. All factors had a negligible impact on the base case results. Overall, the deterministic sensitivity analyses produces consistent results from the decision uncertainty point of view.

Table 47 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case			[redacted]	0.470	[redacted]
Choice of parametric modelling	Gompertz instead of KM + Gompertz tail	Full parametric	[redacted]	0.458	[redacted]
	Log-normal instead of KM + Gompertz tail	2nd lowest AIC/BIC	[redacted]	0.446	[redacted]
	Generalized gamma instead of KM + Gompertz tail	3rd lowest AIC/BIC	[redacted]	0.448	[redacted]

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Dosing	Planned dose without vial sharing instead on vial sharing	Possible dosing in real life	[redacted]	0.470	[redacted]
Utilities	Hedden et al instead of Lloyd et al		[redacted]	0.517	[redacted]
	Lidgren et al instead of Lloyd et al		[redacted]	0.451	[redacted]
	Paracha et al instead of Lloyd et al		[redacted]	0.464	[redacted]

AIC, Akaike Information Criteria; BIC, Bayesian Information Criterion; ICER, Incremental Cost-Effectiveness Ratio; KM, Kaplan-Meier; QALY, Quality-Adjusted Life-Year

In the scenario analysis we tested additional scenarios related to key assumptions (Table 48). These scenarios are based on different valuations or guidelines rather than natural uncertainty related to a specific parameter. Discount rates and modelling time horizon had the biggest impact on the result. However, across all scenarios the decision uncertainty remains low.

Table 48 Scenario analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case			[redacted]	0.470	[redacted]
General parameters					
Discount rates:	C: 0% E: 0%	Plausible minimum	[redacted]	0.883	[redacted]
Discount rates:	C: 5% E: 5%	Plausible maximum	[redacted]	0.371	[redacted]
Time horizon:	32.8 years	Life expectancy at birth, female (years) in Denmark was reported at 83.8 years in 2023	[redacted]	0.425	[redacted]
Waning effect:	Effect is maintained	Most optimistic assumption	[redacted]	0.483	[redacted]

Tornado diagram summarises meaningful costs parameters in terms on their feasible lowest and highest values. The model in Excel provides extensive number of options and results for DSA and scenario analyses (see sheets “UDSA”, “BDSA” and “Scenario Analyses”. In general, the uncertainty remains low from the decision uncertainty point of view.

Figure 14 Tornado diagram

Although Phesgo is already cost-effective treatment with the list price sensitivity of Phesgo unit price on cost-effectiveness is tested in a separate analysis. Figure 15 shows how the ICER decreases as the list price of Phesgo is discounted. [redacted]

Figure 15 Cost per QALY gained (ICER) for different price levels of Phesgo

12.2.3 Probabilistic sensitivity analyses

Key variables from the parametric uncertainty point of view were included in PSA (see Appendix D).

Figure 16 shows simulated (1000 times) expected values for total costs (DKK and DKK) and QALYs (14.794 and 14.328) for Phesgo and trastuzumab + placebo, respectively. The results indicate that the uncertainty is at the same level for both comparators. That means that there is not only uncertainty related to Phesgo, but also uncertainty regarding how the standard of care (trastuzumab + placebo) performs in terms of expected costs and health benefits.

Figure 16 Simulation results in terms of mean costs and QALYs

Figure 17 shows the incremental cost-effectiveness plane for Phesgo vs trastuzumab + placebo using the base case assumptions. Even though there is some uncertainty around the exact incremental clinical benefit and costs, all 1000 simulations are located in the northeast quadrant with mean ICER of Thus, at the established willingness-to-pay threshold for this disease, it is highly likely that Phesgo is a cost-effective alternative to comparator. This is shown clearly in the cost-effectiveness acceptability curve (Figure 18 which indicate high probability of cost-effectiveness at any reasonable willingness to pay thresholds in Denmark.

Figure 17 Cost-effectiveness plane in terms of incremental costs and QALYs

Figure 18 Cost-effectiveness acceptability curve

The convergence of the simulation (N=1000) in terms of incremental net monetary benefit (NMB) is presented in Figure 19.

Figure 19 Convergence of the simulations

The model was built of APHINITY head-to-head trial. We utilized patient level data from the trial in modelling and in populating the input parameters. These formed a strong basis for modeling.

The uncertainty of the model and results was considered from parameter, structural/modeling, and methodological perspectives and was further considered from the decision uncertainty perspective. Decision uncertainty relates to the risk of making the wrong decision about Phesgo either adopting a technology that does not provide good value or failing to adopt a technology that does. The cost-effectiveness results were generally very robust across scenarios and sensitivity analyses (incl. for instance assumptions related to extrapolations, costs and utilities).

In total, Phesgo added 0.470 QALYs at an incremental cost [redacted], resulting in an ICER of [redacted] DKK using the proposed list price for Phesgo. NMB remained positive at the existing willingness-to-pay threshold of [redacted] DKK for this indication when key model parameters were varied, which indicates low decision uncertainty.

The base case results were based on the public list price. Even with the list price the ICER is clearly below expected willingness to pay threshold in Denmark.

The conclusion of this analysis is therefore that Phesgo is, with very high probability, a cost-effective alternative to trastuzumab + placebo IV and the decision uncertainty is reasonable low.

13. Budget impact analysis

Table 49 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		
Phesgo + chemotherapy	52	54	56	58	60
Trastuzumab + chemeotherapy	0	0	0	0	0
			Non-recommendation		
Phesgo + chemetherapy	0	0	0	0	0
Trastuzumab + chemeotherapy	52	54	56	58	60

Budget impact

Table 50 Expected budget impact of recommending the medicine for the indication (mio. DKK)

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

14. List of experts

Not applicable as no experts have been consulted for this application.

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Appendix A. Main characteristics of studies included

Table 51 Main characteristic of studies included

Trial name:	NCT number:
Objective	The study investigated whether pertuzumab, when added to adjuvant trastuzumab and chemotherapy, improves outcomes among patients with HER2-positive breast cancer in an adjuvant setting
Publications – title, author, journal, year	Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer, Minckwitz Gv et al. N ENGL J MED 377;2, 2017 (19) Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer in the APHINITY Trial: 6 Years' Follow-Up. Piccart M et al. J Clin Oncol. 39, 1448-1457, 2021 (56) Adjuvant Pertuzumab and Trastuzumab in Early Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer in the APHINITY Trial: Third Interim Overall Survival Analysis With Efficacy Update, Loibl S et al. J Clin Oncol. 42(31):3643-3651, 2024 (48)
Study type and design	Completed, Phase 3, randomized multicenter, double-blind, placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo vs chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy in patients with operable HER2-positive primary breast cancer.
Sample size (n)	4805
Main inclusion criteria	• Non-metastatic operable primary invasive HER2-positive carcinoma of the breast that is histologically confirmed, and adequately excised • Eastern Cooperative Oncology Group (ECOG) performance status less than or equal to (</=) 1 • Known hormone receptor status (estrogen receptor and progesterone receptor) • The interval between definitive surgery for breast cancer and the first dose of chemotherapy must be no more than 8 weeks (56 days). The first cycle of chemotherapy must be administered within 7 days of randomization or on Day 56, whichever occurs first • Baseline left ventricular ejection fraction (LVEF) greater than or equal to (>/=) 55 percent (%) measured by echocardiogram (ECHO) or Multiple-Gated Acquisition (MUGA) Scan • Confirmed HER2 positive status • Completion of all necessary baseline laboratory and radiologic investigations prior to randomization

	• Women of childbearing potential and male participants with partners of childbearing potential must agree to use effective contraception (as defined by the protocol) by the participant and/or partner for the duration of the study treatment and for at least 7 months after the last dose of study drug
Main exclusion criteria	• History of any prior (ipsi- and/or contralateral) invasive breast cancer • History of non-breast malignancies within the 5 years prior to study entry, except for carcinoma in situ of the cervix, carcinoma in situ of the colon, melanoma in situ, and basal cell and squamous cell carcinomas of the skin • Any "clinical" T4 tumor as defined by primary tumor/regional lymph nodes/distant metastasis (TNM), including inflammatory breast cancer • Any node-negative tumor • Any previous systemic chemotherapy for cancer or radiotherapy for cancer • Prior use of anti-HER2 therapy for any reason or other prior biologic or immunotherapy for cancer • Concurrent anti-cancer treatment in another investigational trial • Serious cardiac or cardiovascular disease or condition • Other concurrent serious diseases that may interfere with planned treatment including severe pulmonary conditions/illness • Abnormal laboratory tests immediately prior to randomization • Pregnant or lactating women • Sensitivity to any of the study medications or any of the ingredients or excipients of these medications
Intervention	N=2400 Adjuvant treatment with pertuzumab plus trastuzumab in combination with chemotherapy for 1 year (up to 18 cycles) (N=2400). <u>Dosing schedule:</u> Pertuzumab 840 mg IV loading dose followed by 420 mg IV every three weeks (q3w) and trastuzumab 8 mg/kg IV loading dose, followed by 6 mg/kg IV q3w for 1 year (maximum 18 cycles) in combination with 1 of the following IV chemotherapy regimen (anthracycline-based or nonanthracycline-based) per Investigator's choice: 1) 3-4 cycles (Q3W) of 5-fluorouracil 500-600 mg/m^2 + epirubicin 90-120 mg/m^2 or doxorubicin 50 mg/m^2 + cyclophosphamide 500-600 mg/m^2 followed by either 3-4 cycles of docetaxel Q3W (100 mg/m^2 for 3 cycles, 75 mg/m^2 in first cycle and 100 mg/m^2 in subsequent

	cycles, or 75 mg/m^2 for 4 cycles) or 12 cycles of paclitaxel 80 mg/m^2 once weekly (QW) 2) 4 cycles (Q3W) of doxorubicin 60 mg/m^2 or epirubicin 90-120 mg/m^2 + cyclophosphamide 500-600 mg/m^2 followed by either 3-4 cycles of docetaxel Q3W or 12 cycles of paclitaxel QW (as described in Option 1) 3) 6 cycles (Q3W) of docetaxel 75 mg/m^2 + carboplatin area under the curve (AUC) 6 (up to 900 mg).
Comparator(s)	N=2405 Adjuvant treatment with placebo plus Herceptin (for 1 year) in combination with chemotherapy <u>Dosing schedule:</u> Placebo IV infusion q3w and trastuzumab (8 milligrams per kilogram [mg/kg] loading dose, then 6 mg/kg) IV q3w for 1 year (maximum 18 cycles) in combination with 1 of the following IV chemotherapy regimen (anthracycline-based or non-anthracycline-based) per Investigator's choice: 1) 3-4 cycles (Q3W) of 5-fluorouracil 500-600 milligrams per square meter (mg/m^2) + epirubicin 90-120 mg/m^2 or doxorubicin 50 mg/m^2 + cyclophosphamide 500-600 mg/m^2 followed by either 3-4 cycles of docetaxel Q3W (100 mg/m^2 for 3 cycles, 75 mg/m^2 in first cycle and 100 mg/m^2 in subsequent cycles, or 75 mg/m^2 for 4 cycles) or 12 cycles of paclitaxel 80 mg/m^2 QW 2) 4 cycles (Q3W) of doxorubicin 60 mg/m^2 or epirubicin 90-120 mg/m^2 + cyclophosphamide 500-600 mg/m^2 followed by either 3-4 cycles of docetaxel Q3W or 12 cycles of paclitaxel QW (as described in Option 1) 3) 6 cycles (Q3W) of docetaxel 75 mg/m^2 + carboplatin AUC 6 (up to 900 milligrams [mg]).
Follow-up time	Median follow-up of 135.3 months (range 0 - 155)
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** <u>Primary objective/endpoint:</u> IDFS (Invasive Disease-Free Survival), defined as the time from randomization to the first occurrence of one of the following events: • Ipsilateral invasive breast tumor recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion)

- Ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall, and/or skin of the ipsilateral breast)
- Distant recurrence (i.e., evidence of breast cancer in any anatomic site – other than the two above mentioned sites— that was either histologically confirmed or clinically diagnosed as recurrent invasive breast cancer)
- Death attributable to any cause including breast cancer, non-breast cancer, or unknown cause (but cause of death was specified if at all possible)
- Contralateral invasive breast cancer

All second primary non-breast cancers and in situ carcinomas (including ductal carcinoma in situ and Lobular carcinoma in situ) and nonmelanoma skin cancer were excluded as an event in this endpoint. If a patient experienced an event on the same day as randomization their time from randomization to event was set as 1 day. Patients who did not have an event at the time of data analysis were censored at the date they were last known to be alive and event-free.

Note: this definition of IDFS (which excludes second primary non-breast cancers as events) is not the same as IDFS defined by Hudis et al. (2007) (66) (which includes second primary non-breast cancers as events).

Secondary objectives/endpoints:

- Overall survival (OS) defined as the time from randomization to death attributable to any cause. Patients who were alive (including lost to follow-up) at the time of the analysis were censored at the last known alive date.
- HRQoL defined as symptoms of therapy, patient functioning, and global health status and assessed by the EORTC QLQ-C30 and EQ-5D-3L questionnaires

Endpoints not included in this application:

Secondary objectives/endpoints:

- Invasive Disease-Free Survival including second primary non-breast cancer (IDFS-SPNBC) defined in the same way as IDFS but including second primary non-breast invasive cancer as an event (with the exception of non-melanoma skin cancers and in situ carcinoma of any site).
- Disease Free Survival (DFS) defined as the time between randomization and the date of the first occurrence of an invasive disease-free survival event including second primary non-breast cancer events or contralateral or ipsilateral ductal carcinoma in situ. Patients who did not have an event at the time of data analysis were censored at the date last known to be alive and event free.
- Recurrence-Free Interval (RFI) defined as the time between randomization and the date of local, regional or distant breast cancer recurrence. Patients who did not have a recurrence

event at the time of data analysis were censored at the date last known to be alive or at date of death.

- Distant Recurrence-Free Interval (DRFI) defined as the time between randomization and the date of distant breast cancer recurrence. Patients who did not have a distant recurrence event at the time of data analysis were censored at the date last known to be alive or at date of death.
- Secondary endpoint: HRQoL was defined as symptoms of therapy, patient functioning, and global health status and assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, Breast module (EORTC QLQ-BR23) questionnaire.

Exploratory endpoints:

Breast cancer-free interval defined as the time between randomization and the date of local, regional or distant breast cancer recurrence, invasive contralateral breast cancer or ductal carcinoma in situ (contralateral or ipsilateral). Patients who did not have a recurrence event at the time of data analysis were censored at the date when they were last known to be alive or at their date of death.

Safety Variables:

Safety of the treatment was evaluated as a secondary objective as follows:

- Incidence of a symptomatic ejection fraction decrease (otherwise referred to as heart failure) or definite or probable cardiac death
- Incidence of left ventricular systolic dysfunction (LVSD) (defined as an absolute decrease in LVEF of at least 10 percentage points below the baseline measurement and to below 50% absolute value) or an asymptomatic decline in LVEF requiring treatment or leading to discontinuation of study treatment (nonserious adverse event of special interest)
- LVEF measurements over the course of the study;
- Incidence and severity of AEs and SAEs;
- Laboratory test abnormalities.

Primary cardiac endpoints:

Heart failure NYHA Class III or IV and a drop in LVEF of at least 10 EF points from baseline and to below 50%.

Cardiac death (identified by the APHINITY Cardiac Advisory Board), defined as either

- Definite cardiac death: due to heart failure, myocardial infarction or documented primary arrhythmia.
- Probable cardiac death: sudden unexpected death within 24 hours of a definite or probable cardiac event (e.g., syncope,

	cardiac arrest, chest pain, infarction, arrhythmia) without documented etiology *Secondary cardiac endpoints:* Defined as an asymptomatic or mildly symptomatic (NYHA Class II) significant drop in LVEF by MUGA scan or echocardiogram, confirmed by a second LVEF assessment within approximately 3 weeks showing also a significant drop OR as confirmed by the APHINITY Cardiac Advisory Board. A significant LVEF drop is defined as an absolute decrease of at least 10 EF points below the baseline measurement and to below 50%. The assessment of the secondary cardiac endpoint will be based on data from randomization until the start of any new therapy for recurrence of disease. Therefore, any asymptomatic or mildly symptomatic (NYHA Class II) significant drop in LVEF should be confirmed within approximately 3 weeks, even during follow-up phase. *Other Cardiac events:* Acute coronary syndrome, acute myocardial infarction, and severe rhythm disturbances requiring treatment.
Method of analysis	The null hypothesis for the primary endpoint was that the survival distributions of IDFS in the two treatment groups were the same. The alternative hypothesis was that the survival distributions of IDFS in the treatment and the control arm were different: H0: $S_{<pertuzumab>} = S_{<placebo>}$ vs. H1: $S_{<pertuzumab>} \neq S_{<placebo>}$ The study was designed to have 80% power to test the null hypothesis of no true difference in risk of an IDFS event (HR = 1) versus the alternative hypothesis of a difference (HR = 0.75) in HRs with a 5%, 2-sided significance level. Under these assumptions approximately 379 IDFS events were required for the primary analysis of IDFS. Patients who had not had an event at the time of data analysis were censored at the date they were last known to be alive and event-free. The stratified log-rank test was used to compare IDFS between the two treatment arms. The unstratified log-rank test was also conducted as a sensitivity analysis. The Kaplan-Meier approach was used to estimate 3-year and 4-year IDFS rates for each treatment arm. The stratified Cox proportional hazards model was used to estimate the hazard ratio between the two treatment arms and its 95% CI. The primary analysis was based on the ITT population. Cox proportional hazards regression models were performed in an exploratory manner, to determine if adjustment for additional covariates would modify the conclusions from the primary analysis. Variables considered in addition to the stratification factors were other disease- or patient-related prognostic or predictive factors (19).
Subgroup analyses	Subgroup analyses were intended to assess consistency of the overall result in the ITT population and were not powered to detect a

statistically significant effect; nor were the analyses alpha-controlled to protect inflated false-positive risk, as is standard for exploratory subgroup comparisons.

Subgroups for Efficacy Analysis (IDFS and OS)

Subgroup analyses were performed for the primary endpoint IDFS and the secondary endpoints OS and DRFI. Pre-defined subgroups of interest were the randomization stratification factors using the following categories:

Nodal status: 0 positive nodes and tumor ≤ 1 cm[a]; 0 positive nodes and tumor >1 cm[a]; 1-3 positive nodes; ≥4 positive nodes.

Adjuvant chemotherapy regimen: Anthracycline containing regimen; Non-anthracycline containing regimen.

Hormone receptor status[b]: ER and PR negative; ER and/or PR positive[c].

Geographical region: USA; Canada/Western Europe/Australia-New Zealand/South Africa; Eastern Europe; Asia-pacific; Latin America.

Protocol version[d]*:* Protocol A; Protocol Amendment B

[a] *Nodal status could take any of these four categories under Protocol A, but only the two categories with positive nodes after Protocol Amendment B were implemented.*

[b] *Hormone receptor status had to be known for each patient and was confirmed by the central laboratory. Hormone receptor status ('negative' or 'positive') followed the American Society Clinical Oncology College of American Pathologists guidelines (80).*

[c] *ER or PR positive was defined as ≥1% immunoreactive cells.*

[d] *Protocol Version was introduced as a stratification factor at the time Protocol Amendment B was issued (closure of recruitment to patients with node-negative disease).*

as well as the following disease- or patient-related prognostic or predictive factors.

- Nodal status categorized as 0 positive nodes vs. ≥ 1 positive nodes
- Central hormonal receptor status (ER-positive PR-positive; ER-positive PgRnegative;
- ER-negative PR-positive; ER-negative PR-negative)
- Menopausal status at screening (pre-menopausal; post-menopausal)
- Age (<40, 40-49, 50-64, <65, ≥ 65)
- Histological grade (Grade 1; Grade 2; Grade 3)
- Type of surgery for primary tumor (breast-conserving surgery; mastectomy)
- Tumor size (0 - <2 cm; ≥ 2 - 5 cm; ≥ 5 cm)
- Loco-regional radiotherapy (Yes; No)

	• Race (White; Black; Asian; Other) • Sex (female patients; the number of male patients was considered to be insufficient to warrant meaningful subgroup analyses). Patients enrolled in either of the two node-positive strata during Protocol A vs. Protocol Amendment B • HER2 subgroups (these analyses were not described in the protocol or the SAP but were defined prior to database lock). Treatment effect (as determined by HR and 3-year IDFS rate) was estimated separately for the defined subgroups. Exploratory tests of interaction between treatment effect and subgroup (at a 10% significance level) were reported using Cox proportional hazards models (43, 63). Also refer to Figure 20 and Table 52 Summary of Time to First IDFS Event (Months) by Subgroup and Treatment Regimen
Other relevant information	Not applicable

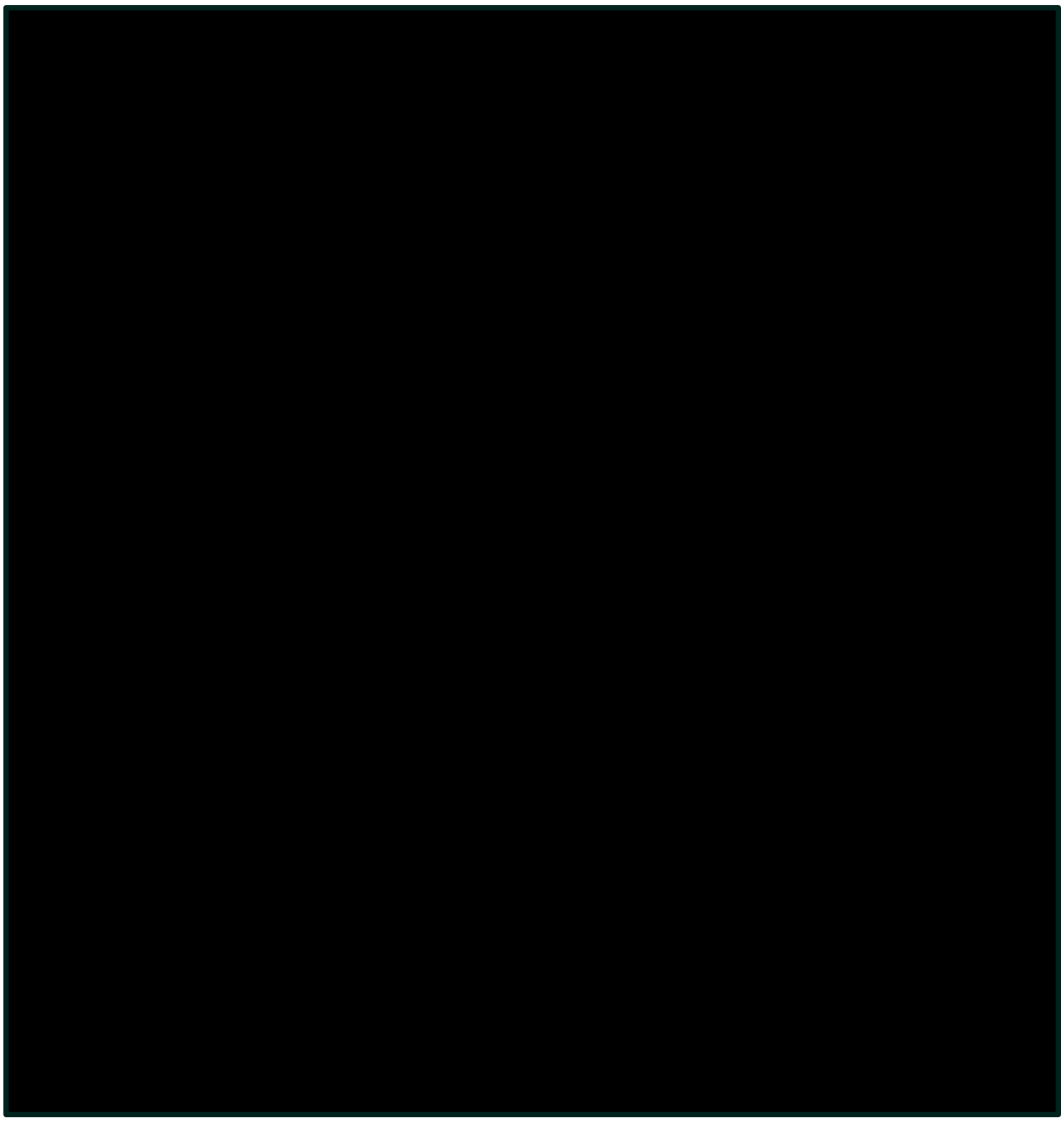

Figure 20 Forest Plot of Time to First IDFS Event (Months) by Subgroup, N+ Population, APHINITY (67)

Table 52 Summary of Time to First IDFS Event (Months) by Subgroup and Treatment Regimen

		Ptz+H+Chemo (N=2400)			Pla+H+Chemo (N=2400)				
		Patients per Group	**N events**	**10 Year KM**	**Patients per Group**	**N events**	**10 Year KM**	**Hazard Ratio**	**95% CI**
All		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nodal Status	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjuvant Chemotherapy Regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Central Hormone Receptor Status	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Protocol Version	[redacted]								
	[redacted]								
Region	[redacted]								
	[redacted]								
	[redacted]								
	[redacted]								
	[redacted]								
Central ER/PR Status	[redacted]								
	[redacted]								
	[redacted]								
	[redacted]								
Menopausal Status at screening	[redacted]								
	[redacted]								
Age group (years)	[redacted]								
	[redacted]								

Histological Grade									
Surgery Type for primary tumor									
Tumor Size (cm)									
Loco-regional radiotherapy									
Race									

Sex									
Protocol Version node positive									

Appendix B. Efficacy results per study

Results per study

Efficacy data presented in Table 53 are limited to the node-positive population, as the treatment effect was predominantly observed in this subgroup based on the IDFS and OS results.

Table 53 Results per study

Results of [trial name (NCT number)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
IDFS (Invasive Disease-Free Survival) 3 years	Ptz+H+Chemo	1503	92.0% (90.59, 93.40)	1.8	Not estimated	Not estimated	HR: 0.77	0.62, 0.96	0.02	IDFS was estimated using the Kaplan–Meier method. Differences between treatment groups were assessed with a stratified log-rank test, and the HR with 95% CI was estimated using a stratified Cox proportional hazards model.	(63)
	Pla+H+Chemo	1502	90.2% (88.63, 91.69)								(63)
IDFS (Invasive Disease-Free Survival) 10 years	Ptz+H+Chemo	1503	84.58% (82.68, 86.49)	5.04	Not estimated	Not estimated	HR: 0.74	0.62, 0.88	0.0006	IDFS was estimated using the Kaplan–Meier method. Differences between treatment groups were assessed with a stratified log-rank test, and the HR with 95% CI was estimated using a stratified Cox proportional hazards model.	(43)
	Pla+H+Chemo	1502	79.55% (77.43, 81.67)								(43)

Results of [trial name (NCT number)]											
				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**		
OS (Overall survival) 10 years	Ptz+H+Chemo	1503	89.55% (97.93, 91.17)	2.68	Not estimated Not estimated	Not estimated Not estimated	HR: 0.79	0.64, 0.79	0.0261	OS was estimated using the Kaplan–Meier method. Differences between treatment groups were assessed with a stratified log-rank test, and the HR with 95% CI was estimated using a stratified Cox proportional hazards model.	(43)
	Pla+H+Chemo	1502	86.87% (85.08, 88.66)								(43)

Appendix C. Comparative analysis of efficacy

N/A

Table 54 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		

Appendix D. Extrapolation

D.1 Extrapolation of IDFS

D.1.1 Data input

Refer to section 8

D.1.2 Model

Refer to section 8

D.1.3 Proportional hazards

Figure 21 Log-log survival plot

Figure 22 Schoenfelt plot

Figure 23 Smoothed hazards plot

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

Table 55 AIC and BIC values across different distributions (final CCOD 11.3 years).

	AIC		BIC	
	Ptz+H+Chemo	Pla+H+Chemo	Ptz+H+Chemo	Pla+H+Chemo
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]

	AIC		BIC	
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]

D.1.5 Evaluation of visual fit

Refer to section 8

D.1.6 Evaluation of hazard functions

Figure 24 IDFS Hazard rate and survival plots considered for

D.1.7 Validation and discussion of extrapolated curves

Refer to section 8

D.1.8 Adjustment of background mortality

Refer to section 8

D.1.9 Adjustment for treatment switching/cross-over

Refer to section 8

D.1.10 Waning effect

Refer to section 8

D.1.11 Cure-point

To support the assumption that patients remaining disease-free for 10 years (120 months) reach a state where mortality risk converges with the background population, we utilised recent clinical evidence on high-risk HER2+ population (54) and Roche's APHINITY clinical trial

1. Defining the High-Risk population and relapse risk

The assumption of cure at 120 months is grounded in the distinct relapse trajectory of high-risk HER2+ eBC:

- **Identification of High-Risk:** Clinical evidence (54) defines high-risk patients primarily by nodal involvement (N1–3) or large tumor size (>5 cm). This aligns with the N+ subgroup of particular interest to the DMC.
- **The critical recurrence window:** Despite HER2+ directed therapies, up to 20% of high-risk patients experience recurrence within 8 years. However, this risk is heavily concentrated in the early years (first 2-3 years) (54).
- **Timing of metastasis:** In high-risk populations, the median time from eBC diagnosis to the development of incurable metastatic disease (mBC) is **23 months (54)**. This supports the model's structure where the "excess risk" is highest in the first 2–3 years and diminishes significantly as patients approach the 10-year mark.

2. Statistical convergence and the "incurability" threshold

The transition to a "cure" assumption at 120 months reflects the biological shift in survivors:

- **Aggressive biology and metastasis:** Recurrent HER2+ disease is aggressive and prone to metastasis; once distant recurrence occurs, the disease is considered incurable.
- **Survival disparity:** High-risk patients have a significantly lower 5-year OS probability (87%) compared to non-high-risk patients (92%).
- **Rationale for cure:** If a high-risk patient avoids recurrence for 120 months—well beyond the median 23-month window for metastatic progression—their biological risk profile has stabilised. At this stage, their probability of death is more accurately represented by background population mortality rather than a residual risk of an aggressive, incurable metastatic event.

3. Alignment with empirical data from APHINITY

- **Preserving data integrity:** The APHINITY study provides empirical follow-up to 156 months. Starting the cure adjustment at 120 months ensures the model respects the observed data during the period where high-risk events are most likely to occur.
- **Avoidance of Conservative Bias:** Without a cure assumption, the model would unfairly apply the "high-risk" excess mortality (evidenced by the 87% 5-year OS) to patients who have already successfully remained disease-free

for a decade. This would lead to clinically implausible long-term survival estimates.

D.2Extrapolation of [effect measure 2]

N/A.

Appendix E. Serious adverse events

In this appendix SAEs from the APHINITY study (CCOD 19 Dec 2016) are listed in Table 56. For frequency counts by PT, multiple occurrences of the same AE in an individual is counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately. The table includes AEs with onset from first dose of any study treatment through 28 days after last dose of study treatment.

Table 56 Serious adverse events, APHINITY, Safety Evaluated Population. CCOD 19 Dec 2016.

MedDRA System Organ Class MedDRA Preferred Term	Ptz+H+Chemo (N=2364) (19, 63)	Pla+H+Chemo (N=2405) (19, 63)
[redacted]		
Febrile neutropenia	208 (8.8%)	196 (8.2%)
[redacted]		

MedDRA System Organ Class MedDRA Preferred Term	Ptz+H+Chemo (N=2364) (19, 63)	Pla+H+Chemo (N=2405) (19, 63)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

MedDRA System Organ Class MedDRA Preferred Term	Ptz+H+Chemo (N=2364) (19, 63)	Pla+H+Chemo (N=2405) (19, 63)
[redacted]		

MedDRA System Organ Class MedDRA Preferred Term	Ptz+H+Chemo (N=2364) (19, 63)	Pla+H+Chemo (N=2405) (19, 63)
[redacted]		
Diarrhoea	58 (2.5%)	18 (0.7%)
[redacted]		

MedDRA System Organ Class MedDRA Preferred Term	Ptz+H+Chemo (N=2364) (19, 63)	Pla+H+Chemo (N=2405) (19, 63)
[redacted]		

MedDRA System Organ Class MedDRA Preferred Term	Ptz+H+Chemo (N=2364) (19, 63)	Pla+H+Chemo (N=2405) (19, 63)
[redacted]		
Pyrexia	39 (1.7%)	45 (1.9%)
[redacted]		

MedDRA System Organ Class MedDRA Preferred Term	Ptz+H+Chemo (N=2364) (19, 63)	Pla+H+Chemo (N=2405) (19, 63)
[redacted]		

MedDRA System Organ Class MedDRA Preferred Term	Ptz+H+Chemo (N=2364) (19, 63)	Pla+H+Chemo (N=2405) (19, 63)
[redacted]		

MedDRA System Organ Class MedDRA Preferred Term	Ptz+H+Chemo (N=2364) (19, 63)	Pla+H+Chemo (N=2405) (19, 63)
[redacted]		

MedDRA System Organ Class MedDRA Preferred Term	Ptz+H+Chemo (N=2364) (19, 63)	Pla+H+Chemo (N=2405) (19, 63)
[redacted]		

MedDRA System Organ Class MedDRA Preferred Term	Ptz+H+Chemo (N=2364) (19, 63)	Pla+H+Chemo (N=2405) (19, 63)
[redacted]		

MedDRA System Organ Class MedDRA Preferred Term	Ptz+H+Chemo (N=2364) (19, 63)	Pla+H+Chemo (N=2405) (19, 63)
[redacted]		

MedDRA System Organ Class MedDRA Preferred Term	Ptz+H+Chemo (N=2364) (19, 63)	Pla+H+Chemo (N=2405) (19, 63)
[redacted]		

MedDRA System Organ Class MedDRA Preferred Term	Ptz+H+Chemo (N=2364) (19, 63)	Pla+H+Chemo (N=2405) (19, 63)
[redacted]		

MedDRA System Organ Class MedDRA Preferred Term	Ptz+H+Chemo (N=2364) (19, 63)	Pla+H+Chemo (N=2405) (19, 63)
[redacted]		

MedDRA System Organ Class MedDRA Preferred Term	Ptz+H+Chemo (N=2364) (19, 63)	Pla+H+Chemo (N=2405) (19, 63)
[redacted]		

Investigator text for SAEs encoded using MedDRA v19.1.

Percentages are based on N in the column headings.

Table 57 Overview of Grade 3-5 events, APHINITY, Safety Evaluated Population. CCOD 19 Dec 2016

MedDRA System Organ Class MedDRA Preferred Term	Ptz+H+Chemo (N=2364) (19, 63)	Pla+H+Chemo (N=2405) (19, 63)
BLOOD AND LYMPHATIC SYSTEM disorder		
[redacted]		
Neutropenia	385 (16.3%)	377 (15.7%)

Febrile Neutropenia	286 (12.1%)	266 (11.1%)
Anaemia	163 (6.9%)	113 (4.7%)
[redacted]		
Neutrophil Count Decreased	228 (9.7%)	230 (9.6%)
[redacted]		

GASTROINTESTINAL DISORDERS		
Diarrhoea	232 (9.8%)	90 (3.7%)

[redacted]

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS

[redacted]

METABOLISM AND NUTRITION DISORDERS

[redacted]

NERVOUS SYSTEM DISORDERS

[redacted]

[redacted]

SKIN AND SUBCUTANEOUS TISSUE DISORDERS

[redacted]

[redacted]

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS

[redacted]

[redacted]

VASCULAR DISORDERS

[redacted]

[redacted]		

REPRODUCTIVE SYSTEM AND BREAST DISORDERS

[redacted]		

INJURY, POISONING AND PROCEDURAL COMPLICATIONS

[redacted]		

[redacted]

CARDIAC DISORDERS

[redacted]

[redacted]

PSYCHIATRIC DISORDERS

[redacted]

IMMUNE SYSTEM DISORDERS

[redacted]

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED

[redacted]

[redacted]

RENAL AND URINARY DISORDERS

[redacted]

HEPATOBILIARY DISORDERS

[redacted]

[redacted]

EAR AND LABYRINTH DISORDERS

[redacted]

EYE DISORDERS

[redacted]

ENDOCRINE DISORDERS

[redacted]

[redacted]

CONGENITAL, FAMILIAL AND GENETIC DISORDERS

[redacted]

PRODUCT ISSUES

[redacted]

SURGICAL AND MEDICAL PROCEDURES

[redacted]

PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS

[redacted]

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately. Table includes AEs with onset from first dose of any study treatment through 28 days after last dose of study treatment.

Appendix F. Health-related quality of life

F.1 Presentation of the health-related quality of life measured by EORTC QLQ-C30

F.1.1 Study design and measuring instrument – EORTC QLQ-C30

The APHINITY study design is described in section 6.1.1.
Secondary objectives of the study included HRQoL measured by the EORTC QLQ-C30 v 3.0 instrument in patients treated with Ptz+H+Chemo and Pla+H+Chemo (57).

EORTC QLQ-C30 is a general instrument designed to assess overall functioning and symptom impact in patients with cancer and consists of 30 questions that assess 5 aspects of patient functioning (physical, emotional, role, cognitive, and social), symptom scales: (fatigue, nausea and vomiting, pain; and the global health/quality of life) and single-items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) (81). Results from the global health/quality of life domain will be presented in this appendix.

The EORTC QLQ-C30 instrument were scored according to the EORTC Scoring Manual (82). All scale scores range from 0 to 100. Higher scores on the functional and general health status scales indicate better health. Higher scores on the symptom scales indicate more severe symptoms. The PRO endpoints were not included in the hierarchical testing strategy but changes from baseline were defined as clinically meaningful if they differed by ≥ 10 points (83).

F.1.2 Data collection - EORTC QLQ-C30

EORTC QLQ-C30 assessments was conducted at baseline; “Week 13”, Week 25; treatment completion; and during post-treatment follow-up at 18, 24 and 36 months. The time point denoted as “Week 13” corresponds to the end of taxane treatment in all patients, and the actual time of this assessment depends on the type of chemotherapy. For patients receiving anthracycline-based chemotherapy, the actual time point was Week 10 or Week 13 of HER2-targeted treatment (depending on the chemotherapy regimen given). For patients receiving non-anthracycline-based chemotherapy (i.e., the Ptz+TCH regimen), this was Week 19 of HER2-targeted treatment.

Data was collected in the ITT population and included patients who were ongoing in the study at the expected date of the scheduled visit and had not experienced disease recurrence. Patients completed the questionnaires at the center prior to physician assessment and prior to receiving study treatment. A key person at each center, such as

a research nurse, was recommended to be responsible for data collection to ensure high compliance and data completeness.

The EORTC QLQ-C30 questionnaires were considered completed if at least 50% of questions had been answered. Completion rates for EORTC QLQ-C30 were consistently high throughout the study with more than 85.0% of PRO-evaluable patients completing at least one question at each of the scheduled assessments.

Completion rates were comparable across treatment arms and between anthracycline/non-anthracycline chemotherapies (57). Therefore, completion rates and results are reported for all patients.

Table 58 Pattern of missing data and completion, EORTC-QLQ-C30, ITT population. CCOD 19 Dec 2016 (57).

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Ptz+H+Chemo				
Baseline	2400	62 (3%)	2400	2338 (97%)
Week 13*	2400	119 (5%)	2239	2120 (95%)
Week 25	2400	91 (4%)	2187	2096 (96%)
End of treatment (Month 12)	2400	289 (12%)	2378	2089 (88%)
Follow-up: Month 18	2400	248 (11%)	2208	1960 (89%)
Follow-up: Month 24	2400	269 (12%)	2169	1900 (88%)
Follow-up: Month 36	2400	235 (11%)	2094	1859 (89%)
Pla+H+Chemo				
Baseline	2404	61 (3%)	2404	2343 (97%)
Week 13*	2404	119 (5%)	2283	2164 (95%)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Week 25	2404	113 (5%)	2237	2124 (95%)
End of treatment (Month 12)	2404	249 (10%)	2391	2142 (90%)
Follow-up: Month 18	2404	284 (13%)	2244	1960 (87%)
Follow-up: Month 24	2404	279 (13%)	2189	1910 (87%)
Follow-up: Month 36	2404	266 (13%)	2097	1831 (87%)

*The time point "Week 13" in this table and the associated programmed outputs corresponds to the end of taxane treatment; the actual time depends on the type of chemotherapy received. For patients receiving non-anthracycline-based chemotherapy (i.e., the Ptz+TCH regimen), this was Week 19 of HER2-targeted treatment.

For EORTC QLQ30 the most frequent reason for missing data at all timepoints were "[redacted]" peaking during the follow-up period (Month 18 and 24). In addition, the explanation "Patient Refused" gradually increased over time, particularly rising at the end of treatment and late follow-up (Month 36). The trends between the two arms are largely consistent. Refer to the Table 59 below. These data are not available EQ-5D.

The number of patients missing data due to reasons potentially linked to patient characteristics (such as 'Patient refused' or 'Patient unavailable') is negligible. Consequently, the number of patients in these subgroups is insufficient to perform a meaningful statistical comparison of baseline characteristics between the two arms.

Table 59 EORTC-QLQ-C30 – recorded explanations for missing completion of at least one question, APHINITY

Recorded explanation for missing completion of at least one question	Ptz+H+Chemo (N=2400)	Pla+H+Chemo (N=2404)
Baseline		
Did not complete at least 1 question	[redacted]	[redacted]
- Patient unavailable	[redacted]	[redacted]
- Patient refused	[redacted]	[redacted]
- Administrative error	[redacted]	[redacted]

Recorded explanation for missing completion of at least one question	Ptz+H+Chemo (N=2400)	Pla+H+Chemo (N=2404)
- Other	[redacted]	[redacted]
- Missing	[redacted]	[redacted]
Week 13		
Did not complete at least 1 question	[redacted]	[redacted]
- Patient unavailable	[redacted]	[redacted]
- Patient refused	[redacted]	[redacted]
- Administrative error	[redacted]	[redacted]
- Other	[redacted]	[redacted]
- Missing	[redacted]	[redacted]
Week 25		
Did not complete at least 1 question	[redacted]	[redacted]
- Patient unavailable	[redacted]	[redacted]
- Patient refused	[redacted]	[redacted]
- Administrative error	[redacted]	[redacted]
- Other	[redacted]	[redacted]
- Missing	[redacted]	[redacted]
End of treatment		
Did not complete at least 1 question	[redacted]	[redacted]
- Patient unavailable	[redacted]	[redacted]
- Patient refused	[redacted]	[redacted]
- Administrative error	[redacted]	[redacted]
- Other	[redacted]	[redacted]
- Missing	[redacted]	[redacted]
FU Month 18		

Recorded explanation for missing completion of at least one question	Ptz+H+Chemo (N=2400)	Pla+H+Chemo (N=2404)
Did not complete at least 1 question	[redacted]	[redacted]
- Patient unavailable	[redacted]	[redacted]
- Patient refused	[redacted]	[redacted]
- Administrative error	[redacted]	[redacted]
- Other	[redacted]	[redacted]
- Missing	[redacted]	[redacted]
FU Month 24		
Did not complete at least 1 question	[redacted]	[redacted]
- Patient unavailable	[redacted]	[redacted]
- Patient refused	[redacted]	[redacted]
- Administrative error	[redacted]	[redacted]
- Other	[redacted]	[redacted]
- Missing	[redacted]	[redacted]
FU Month 36		
Did not complete at least 1 question	[redacted]	[redacted]
Patient unavailable	[redacted]	[redacted]
Patient refused	[redacted]	[redacted]
Administrative error	[redacted]	[redacted]
Other	[redacted]	[redacted]
Missing	[redacted]	[redacted]

F.1.3 HRQoL results - EORTC QLQ-C30

Global health status

Mean global health status scores were [redacted]) in the pertuzumab arm and [redacted]) in the placebo arm at baseline. Scores worsened in both treatment arms up to the end of taxane treatment and returned to baseline

thereafter. No clinically meaningful differences were seen at any time point in either arm.

Table 60 HRQoL EORTC-QLQ-C30 summary statistics - Global Health Status , ITT population. CCOD 19 Dec 2016 (57)

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI), p-value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 13*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment (Month 12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up: Month 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up: Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up: Month 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CCOD, clinical cut-off date; CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HRQoL, Health Related Quality of Life; ITT, intent-to-treat; SE, standard error

Figure 25 EORTC QLQ–C30 Global Health Status: Change from Baseline by Visit, ITT population: CCOD, 19 Dec 2016CCOD, clinical cut-off date; FU, Follow-up, ITT, intent-to-treat

Appendix G. Probabilistic sensitivity analyses

Parameters, values and distributions used in PSA are reported in **Table 61**. Model detailed information is available in the Excel model sheets.

Table 61. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
IDFS parameter estimates of parametric survivor functions	Different for all distributions (see model sheet "IDFS Parameters")	Different for all distributions (see model sheet "IDFS Parameters")	Different for all distributions (see model sheet "IDFS Parameters")	Sensitivity/ scenario analyses comparing alternative tail distributions.
HSUV				
Utility values for IDFS, remission, non-metastatic recurrence and metastatic				
IDFS - On chemotherapy	[redacted]	Not reported (see model sheet "Utility Values")	Not reported (see model sheet "Utility Values")	A beta distribution has been used to sample all these utilities in the probabilistic sensitivity analysis.
IDFS - On treatment / off chemotherapy	[redacted]			
IDFS - Off treatment	[redacted]			In the PSA sampling is done independently for intervention and comparator.
Locoregional recurrence	[redacted]			
Remission	[redacted]			
1st line metastatic	0.773			
2nd line+ metastatic	0.520			
Costs				
Informal care cost per hour (DKK)	188	150.4	225.6	Parameter was modeled using a log-normal distribution, with the standard deviation calculated using the

				formula (LN(upper bound) - LN(lower bound)) / 4. The upper and lower bounds were defined as ±20% of the mean unit cost
Market share in Non metastatic recurrence health state impacting medical costs				
Herceptin IV + docetaxel	5%	5%	5%	Option for gamma distribution but for the PSA but deterministic values are used is also PSA
Herceptin SC + docetaxel	95%	95%	95%	
1st line metastatic health state - Early disease recurrence				
Herceptin IV + docetaxel	10.0%	10.0%	10.0%	Option for gamma distribution but for the PSA but deterministic values are used is also PSA
Herceptin SC + docetaxel	24.0%	24.0%	24.0%	
Trastuzumab bx+ docetaxel	0.0%	0.0%	0.0%	
Kadcyla	0.0%	0.0%	0.0%	
Trastuzumab deruxtecan	66.0%	66.0%	66.0%	
1st line metastatic health state – Late disease recurrence – PHT arm				
Perjeta + trastuzumab + docetaxel	0.0%	0.0%	0.0%	Option for gamma distribution but for the PSA but deterministic values are used is also PSA
Herceptin IV + docetaxel	0.0%	0.0%	0.0%	
Herceptin SC + docetaxel	0.0%	0.0%	0.0%	
trastuzumab bx+ docetaxel	22.9%	22.9%	22.9%	
Docetaxel	5.9%	5.9%	5.9%	

Phesgo	71.2%	71.2%	71.2%	
1st line metastatic health state – Late disease recurrence – HT arm				
Perjeta + trastuzumab + docetaxel	71.2%	71.2%	71.2%	Option for gamma distribution but for the PSA but deterministic values are used is also PSA
Herceptin IV + docetaxel	0.0%	0.0%	0.0%	
Herceptin SC + docetaxel	0.0%	0.0%	0.0%	
trastuzumab bx+ docetaxel	22.9%	22.9%	22.9%	
Docetaxel	5.9%	5.9%	5.9%	
2nd line+ metastatic health state- Early disease recurrence				
Kadcyla	67.0%	67.0%	67.0%	Option for gamma distribution but for the PSA but deterministic values are used is also PSA
Herceptin IV + capecitabine	5.0%	5.0%	5.0%	
Herceptin SC + capecitabine	11.0%	11.0%	11.0%	
Trastuzumab bx+ capecitabine	0.0%	0.0%	0.0%	
Capecitabine	17.0%	17.0%	17.0%	
Trastuzumab deruxtecan	0.0%	0.0%	0.0%	
2nd line+ metastatic health state - Late disease recurrence				
Kadcyla	0.0%	0.0%	0.0%	Option for gamma distribution but for the PSA but deterministic values are used is also PSA
Herceptin IV + capecitabine	0.0%	0.0%	0.0%	
Herceptin SC + capecitabine	0.0%	0.0%	0.0%	

Trastuzumab bx+ capecitabine	20.0%	20.0%	20.0%
Lapatinib + capecitabine	0.0%	0.0%	0.0%
Capecitabine	0.0%	0.0%	0.0%
Trastuzumab deruxtecan	80.0%	80.0%	80.0%

Administration cost

Phesgo / all SC products	204.50	163.60	245.40	Parameter was modeled using a log-normal distribution, with the standard deviation calculated using the formula (LN(upper bound) - LN(lower bound)) / 4. The upper and lower bounds were defined as ±20% of the mean unit cost
Trastuzumab / all IV products	2136.00	1708.80	2563.20	Parameter was modeled using a log-normal distribution, with the standard deviation calculated using the formula (LN(upper bound) - LN(lower bound)) / 4. The upper and lower bounds were defined as ±20% of the mean unit cost

Appendix H. Literature searches for the clinical assessment

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

This application is based on the head-to-head study, APHINITY (BO25126), which compares Ptz+H+chemo with Pla+H+chemo for the adjuvant treatment of HER2-positive early breast cancer with high risk of recurrence. In Danish clinical practice, trastuzumab+chemo is used in the adjuvant setting for the group of patients with N+ disease and pCR that have not received chemotherapy in combination with trastuzumab and pertuzumab in the neoadjuvant setting. Therefore, it is considered a relevant comparator, and a literature review has not been conducted and thus this appendix is not applicable

Table 62 Bibliographic databases included in the literature search

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

Abbreviations:

Table 63 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search

Abbreviations:

Table 64 Conference material included in the literature search

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

H.1.1 Search strategies

N/A

Table 65 of search strategy table for [name of database]

No.	Query	Results
#1		88244

H.1.2 Systematic selection of studies

N/A

Table 66 Inclusion and exclusion criteria used for assessment of studies

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

Table 67 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study 1						

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

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

This application is based on the head-to-head study, APHINITY (BO25126), which compares Ptz+H+chemo with Pla+H+chemo for the adjuvant treatment of HER2-positive early breast cancer with high risk of recurrence. In Danish clinical practice, trastuzumab+chemo is used in the adjuvant setting for the group of patients with N+ disease and pCR that have not received chemotherapy in combination with trastuzumab and pertuzumab in the neoadjuvant setting. Therefore, it is considered a relevant comparator, and a literature review has not been conducted and thus this appendix is not applicable.

Table 68 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion

Abbreviations:

Table 69 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search

Table 70 Conference material included in the literature search

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

I.1.1 Search strategies

N/A

Table 71 Search strategy for [name of database]

No.	Query	Results
#1		88244

Literature search results included in the model/analysis:

N/A

I.1.2 Quality assessment and generalizability of estimates

N/A

I.1.3 Unpublished data

N/A

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

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

This application is based on the head-to-head study, APHINITY (BO25126) which compares Ptz+H+chemo with Pla+H+chemo for the adjuvant treatment of HER2-positive early breast cancer with high risk of recurrence. In Danish clinical practice, trastuzumab+chemo is used in the adjuvant setting for the group of patients with N+ disease and pCR that have not received chemotherapy in combination with trastuzumab and pertuzumab in the neoadjuvant setting. Therefore, it is considered a relevant comparator, and a literature review has not been conducted and thus this appendix is not applicable. Modelling of subsequent treatments is also based on drugs that is owned by Roche, and thus we know that this is the only relevant phase 3 pivotal study of these drugs, and thus literature review has not been conducted. The only exception is the modelling on Enhertu as subsequent treatment lines. This has recently been introduced to the Danish treatment based on a Phase 3 trial that is the basis for the analysis. No newer or better quality is available for the treatment on Enhertu. Thus literature review has not been conducted.

J.1.1 Example: Systematic search for […]

N/A

Table 72 Sources included in the search

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

Abbreviations:

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

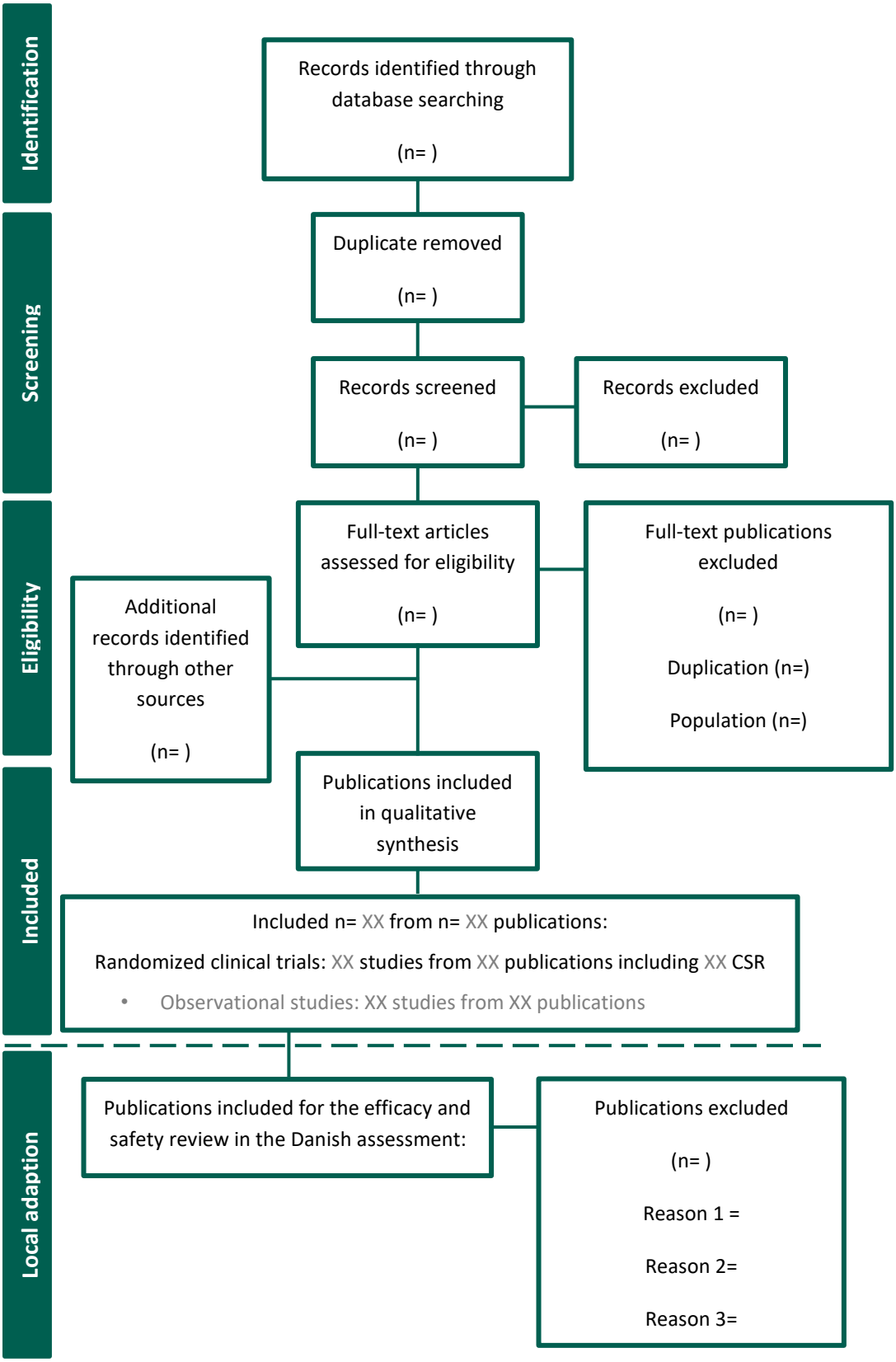
N/A

Table 73 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
e.g. NICE			

Abbreviations:

Example of PRISMA diagram. The diagram is editable and may be used for recording the records flow for the literature searches and for the adaptation of existing SLRs.



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