Medicinrådet

Bilag til Medicinrådets vurdering af rucaparib til 1. linje vedligeholdelses-behandling af avanceret kræft i æggestokkene, æggelederne eller primær kræft i bughinden

- For patienter med epitelcelle highgrade karcinom karcinom og homolog rekombinationsdefekt (HRD+), men uden BRCA1/2-mutation

Vers. 1.0

Bilagsoversigt

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

Medicinrådet
Dampfærgevej 21-23, 3. sal
2100 København Ø

30.03.2026

Re: Draft recommendation of the Danish Medical Council regarding rucaparib for First line maintenance treatment of advanced ovarian cancer in the non-tBRCA HRD+ population

Thank you for the opportunity to provide comments on the draft recommendation for rucaparib for First line maintenance treatment of advanced ovarian cancer.

pharma& agrees with the Medical Council's assessment of the model type and model structure, population, intervention, comparator, efficacy, and safety. With respect to the Council's assessment of PFS and OS, pharma& notes that, in the non-tBRCA HRD+ population, the MAIC analysis showed numerically favorable results for rucaparib versus niraparib, although these differences did not reach statistical significance. As an established indirect treatment comparison method used when head-to-head data are unavailable, MAIC provides clinically relevant comparative evidence; however, the absence of statistical significance in this analysis should not be interpreted as demonstrating therapeutic equivalence, interchangeability, or comparable clinical performance between the treatments.

As stated in the rucaparib SmPC, weekly blood count checks are not required in patients treated with rucaparib.[1] A complete blood count is recommended before starting treatment with rucaparib and monthly thereafter.[1] This differs from what is stated in the niraparib SmPC which recommends `*testing complete blood counts weekly for the first month*`[2].

In the cost comparison, the Medical Council notes that the monitoring frequency for rucaparib does not differ from niraparib and therefore the same monitoring frequency is applied for both arms, which differs from statements in the respective SmPCs[1,2]. The Medical Council also notes in their assessment of safety that hematological adverse events appear to be more frequent with niraparib compared to rucaparib; this further highlights potential differences in monitoring requirements between rucaparib and niraparib.

Rucaparib offers flexibility in terms of dose adjustments[1], which the Medical Council noted may have practical advantages. In ATHENA-MONO, rucaparib demonstrated a high median dose intensity of 88% vs placebo (100%)[3], compared to median dose intensity of 63% for niraparib vs placebo (99%)[4], reflecting less dosing adjustments.
For rucaparib, no adjustments of the starting dose are necessary in patients with mild or moderate hepatic or renal impairment.[1] Furthermore, rucaparib demonstrated a significant improvement in progression-free survival in patients with newly diagnosed advanced ovarian cancer, irrespective of BRCA or HRD status.[3]

pharma& acknowledges that the indirect comparison did not demonstrate statistically significant differences in efficacy and safety outcomes between rucaparib and niraparib. However, a lack of statistical significance should not be taken to establish comparable efficacy or safety, as such conclusions require a study specifically designed to demonstrate non-inferiority or equivalence using pre-specified margins rather than being inferred from a non-significant result. pharma& also disagrees that monitoring requirements would be expected to be aligned between rucaparib and niraparib, in light of (1) the monitoring recommendations set out in the respective SmPCs,[1,2] (2) the frequency of dose adjustments observed in clinical trials, as reflected in the RDI,[3,4] and (3) the differences in hematological adverse events noted by the Medical Council. Treatment with rucaparib would

therefore be associated with less monitoring[1] and, consequently, lower monitoring costs than niraparib[2].

We look forward the receiving the Medical Council's final decision on the rucaparib application.

Kind regards,

Virginie Lavaud (Mar 30, 2026 23:03:11 GMT+2)

References:

1. European Medicines Agency. Rubraca (rucaparib): EPAR – Product Information [Internet]. London: EMA; o.J. Available from: https://www.ema.europa.eu/en/documents/product-information/rubraca-epar-product-information_en.pdf. Accessed 27 Mar 2026.
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3. Monk, BJ et al. A Randomized, Phase III Trial to Evaluate Rucaparib Monotherapy as Maintenance Treatment in Patients With Newly Diagnosed Ovarian Cancer (ATHENA–MONO/GOG-3020/ENGOT-ov45). J Clin Oncol 40, 3952-3964(2022).
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27.03.2026

DBS/LSC

Forhandlingsnotat

Dato for behandling i Medicinrådet	29.04.2026
Leverandør	GHN Pharma
Lægemiddel	Rubraca (rucaparib)
Ansøgt indikation	Rucaparib til 1. linje vedligeholdelsesbehandling af patienter med avanceret HRD+ kræft i æggestokkene, æggelederne eller bughinden, for patienter som ikke har breast cancer gene (BRCA)-mutation (BRCAwt).
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende priser på Rubraca (rucaparib)

Tabel 1: Aftalepris

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Aftalepris SAIP (DKK) pr. 01.04.2026	Rabat ift. AIP
Rubraca	200 mg (60 stk.)	18.075,00	[redacted]	[redacted]
Rubraca	250 mg (60 stk.)	19.075,00	[redacted]	[redacted]
Rubraca	300 mg (60 stk.)	20.075,00	[redacted]	[redacted]

Aftaleforhold

[redacted] Rubraca indgår i et udbud sammen med Lynparza (olaparib) og Zejula (niraparib), som har aftalestart den 01.04.2026 og løber indtil den 31.03.2027 med mulighed for at forlængelse.

Konkurrencesituationen

Rubraca er vurderet til HRD+/BRCAwt patienter, hvor der i dag ikke er en behandlingsvejledning. Tidligere er Zejula samt Lynparza + bevacizumab blevet godkendt til denne indikation. I vurderingsrapporten er Zejula komparator.X

Medicinrådet har udarbejdet en behandlingsvejledning, omkostningsanalyse og lægemiddelrekommandation vedr. lægemidler til BRCA-muteret kræft i æggestokkene, æggelederne eller primær kræft i bughinden, hvor Rubraca, Zejula og Lynparza er vurderet klinisk ligeværdige til patienter med *somatisk* BRCA-muteret kræft i æggestokkene. For patienter med *arvelig* BRCA-muteret kræft i æggestokkene vurderer Medicinrådet, at Lynparza er en bedre behandling end Zejula og Rubraca.

Tabel 2 viser en sammenligning af lægemiddeludgifter pr. patient pr. år i relation til de andre lægemidler.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient pr. 01.04.2026.

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning pr.01.04.2026 (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Rubraca	300 mg (60 stk.)	600 mg, 2 gange dagligt, oral	[redacted]	[redacted]
Lynparza	150 mg (56 stk.)	300 mg, 2 gange dagligt, oral	[redacted]	[redacted]
Zejula	100 mg (84 stk.)	200 mg dagligt, oral	[redacted]	[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

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

Opsummering

Prisen i nuværende aftale har sikret Rubraca en placering som 1. valg i lægemiddelrekommandation til nydiagnosticerede patienter med avanceret *somatisk* BRCA-muteret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden (1. linje vedligeholdelsesbehandling).

Medicinrådet

Instructions for companies

This is the template for submitting evidence to the Danish Medicines Council (DMC) as part of the appraisal process for a new medicinal product or a new indication for an existing medicine. The template is not exhaustive.

Please note the following requirements:

- When preparing their application, companies must adhere to the current version of the DMC's methods guide.
- Always use the current (latest updated) version of this template downloadet from the DMC's website.
- Headings, subheadings and appendices must not be removed. Tables must not be deleted or edited, unless it is explicitly stated in the text.
- Text in grey and [in brackets] is only for example purposes and must be deleted.
- All sections in the template must be filled in. If a section or an appendix is not applicable, state "not applicable" (N/A) and explain why.
- The main body of the application must not be longer than 100 pages (including the title page, contact information and references – excluding appendices).
- The formatting is not to be altered and all cross-references must work.
- All applications must comply with the general data protection regulations, find more information on DMC's data policy here.
- Submissions in either Danish or English are accepted.

The assessment process cannot be initiated before all the requirements are met.

Documentation to be submitted

The following documentation must be sent to the DMC's email ansogning@medicinraadet.dk:

- Application in word format*
- Application in PDF format*
- Health economic model including budget impact model in one Excel file, with full access to the programming code. The model must include relevant sheets from the DMC Excel template 'Key figures including general mortality' available on the DMC's website.
- The European Public Assessment Report (EPAR) should be submitted. Send a draft version if the final one is not published at the time of submission, and send the final version as soon as possible.

Confidential information and blinding

The Danish Medicine Council publishes the application (including attachments) on the website together with the recommendation.

The applicant has the option to blind any confidential information in the application incl. appendices.

Medicinrådet

The application and paper/appendices

If there is confidential information in the application or note/appendices, the company must submit two versions of both the application and note/appendices:

- a version for the DMC's case processing, where the confidential information is marked with yellow marking.
- a version for publication on the DMC's website, where the confidential information is blinded with black marking. The DMC publishes this version.

It is the pharmaceutical companies that must ensure that the blinding is sufficient, so that the confidential information cannot be read when the document is edited.

Therefore, the applicant must ensure that the confidential information is sufficiently redacted blinded for publication on the DMC's website. This can be done, for example, by covering the text/information to be redacted with a black marker simultaneously replacing the underlying text with crosses ("XXX"), so that the text/information cannot be read when editing the document.

Read about redaction of confidential information on the DMC's website.

About macros in Excel

Due to IT security requirements, Excel files containing macros must be authorized and signed by the applicant before being submitted to the DMC. Find more information here.

Version log

Version log		
Version	**Date**	**Change**
2.6	1 April 2025	New e-mail address ansogning@medicinraadet.dk is added.
2.5	10 September 2024	Section 3.4 and 3.4.1: new information regarding ATMP (Advanced Therapy Medicinal Products). Section 6.1.1 and 8.1: Updated text regarding data-cut. Section 4, 8, 10 and 12: Clarification regarding cost-minimization analysis.
2.4	5 July 2024	Section 11: Clarification in the text regarding costs and changes in the tables 26 and 30.
2.3	1 June 2024	Clarification regarding redaction of confidential information, clarification regarding EPAR, clarification regarding literature search and changes in the text regarding costs. New information about Joint Nordic assessments has been added.
2.2	3 November 2023	'Pharmaceutical' is exchanged with 'medicine'. Tabel 26 is new.
2.1	1 September 2023	Section 4.2: Updated information about discount rate (The DMC applies a discount rate of 3.5 % for all years) Section 10.1.3: Clarification regarding EQ-5D-5L and Danish preference weights Section 11.1: Updated information about Excel sheet 'Key Figures'
2.0	15 June 2023	New application template
1.3	6 December 2022	Clarification regarding new IT security requirements concerning macros in Excel files has been added, see page 1.
1.2	20 June 2022	Clarification of the introduction, including instructions on how to complete the form.
1.1	9 February 2022	Appendix K and onwards have been deleted (company-specific appendices) Color scheme for text highlighting table added after table of contents Section 6: Specific requirements for literature search Section 7: Stated it explicitly that statistical methods used need to be described

Version log		
		Section 8.3.1: Listed the standard parametric models Section 8.4.1: Added the need for description of quality of life mapping Appendix A: Specified that the literature search needs to be specific for the Danish context and the application Appendices B and D: Stated it explicitly that statistical methods need to be described in the tables in the appendices
1.0	27 November 2020	Application form for assessment made available on the website of the Danish Medicines Council.

Application for the assessment of rucaparib for maintenance treatment of advanced ovarian, fallopian tube, and peritoneal cancer after response to first-line platinum-based chemotherapy

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

Contact information

Contact information	
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Title	
Phone number	[Include country code]
E-mail	

[If a company wishes to use external representation in relation to the application for evaluation of a new medicine / extension of indications, the following power of attorney must be completed and sent to ansogning@medicinraadet.dk.]

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Abbreviations

1L	First line
AE	Adverse event
AFT	Accelerated failure time
AIC	Akaike information criterion
aOC	Advanced ovarian cancer
BIC	Bayesian information criterion
BICR	Blinded independent central review
BRCA	Breast cancer gene
CEM	Cost-effectiveness model
CFI	Chemotherapy-free interval
CI	Confidence interval
DCO	Data cut-off
DGCG	Dansk Gynaekologisk Cancer Gruppe
DMC	Danish Medicines Council
DSA	Deterministic sensitivity analysis
ECOG	Eastern Cooperative Oncology Group
EM	Effect modifier
EMA	European Medicines Agency
EORTC QLQ-C30 Questionnaire	European Organisation of Research and Treatment of Cancer Quality of Life
ESS	Effective sample size
FACT-O TOI	Functional Assessment of Cancer Therapy – Trial Outcome Index
FIGO	International Federation of Gynecology and Obstetrics
FOSI	Ovarian Symptom Index
HR	Hazard ratio

HRD	Homologous recombination deficiency
HRD+	Homologous recombination deficiency-positive
HRD–	Homologous recombination deficiency-negative
HRQoL	Health-related quality of life
HSUV	Health state utility value
invPFS	Investigator-assessed progression-free survival
IPD	Individual patient-level data
ITT	Intention to treat
KM	Kaplan-Meier
LOH	Loss of Heterozygosity
LY	Life year
MAIC	Matching-adjusted indirect comparison
NICE DSU	National Institute for Health and Care Excellence decision support unit
ORR	Overall response rate
OS	Overall survival
PARP	Poly(ADP-ribose) polymerase
PARPi	Poly(ADP-ribose) polymerase inhibitor
PD	Progressive disease
PF	Prognostic factor
PfLY	Progression-free life year
PFS	Progression-free survival
PFS2	Progression-free survival to second progression
PH	Proportional hazards
PRO	Patient-reported outcome
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RDI	relative dose intensity
RS	Routine surveillance
SAE	Serious adverse event
tBRCA	tumour tissue BRCA
TDT	Time to treatment discontinuation
TFST	Time to first subsequent therapy
TSST	Time to second subsequent therapy

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Rubraca®
Generic name	Rucaparib
Therapeutic indication as defined by EMA	Rucaparib as monotherapy for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy(1).
Marketing authorization holder in Denmark	pharmaand GmbH
ATC code	L01XK03
Combination therapy and/or co-medication	No
(Expected) Date of EC approval	The marketing authorisation for rucaparib in the above-described indication was approved by the European Medicines Agency (EMA) in November 2023.
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	Rucaparib as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy(1).
Other indications that have been evaluated by the DMC (yes/no)	No
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? No Is the product suitable for a joint Nordic assessment? No

Overview of the medicine	
	If no, why not? The submissions to different countries were made at different times.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Rucaparib is supplied in plastic bottles, each containing 60 film-coated tablets (200 mg, 250 mg or 300 mg)(1).

2. Summary table

Summary	
Indication relevant for the assessment	The indication relevant for this submission is a subgroup of the EMA indication: first-line maintenance treatment of advanced cancer of the ovaries, fallopian tubes or primary cancer of the peritoneum for patients with epithelial cell highgrade carcinoma and homologous recombination defect (HRD+), but without BRCA1/2 mutation.
Dosage regiment and administration	Rucaparib is provided as a film-coated tablet. The recommended dose of rucaparib is 600 mg (two 300 mg tablets) taken orally twice daily with or without food (1,200 mg total daily dose). Adverse reactions may be managed through dose interruptions and/or dose reductions: 600 mg to 500 mg [two 250 mg tablets twice daily] to 400 mg [two 200 mg tablets twice daily] to 300 mg [one 300 mg tablet twice daily])(1).
Choice of comparator	The relevant comparators for the non-tBRCA, HRD+ population are niraparib and olaparib in combination with bevacizumab(2, 3).
Prognosis with current treatment (comparator)	The 5-year survival rate of patients with epithelial ovarian cancer in Denmark is 36%–40% in patients with stage III disease and 20%–25% in patients with stage IV disease(4). In the HRD+ population, median OS with niraparib in the PRIMA trial was 71.9 months vs.69.8 months with placebo. Median OS in the non-tBRCA HRD+ population was not reported and niraparib did not significantly improve OS over placebo after 5 years follow-up (HR 0.97 [95% CI: 0.62, 1.53])(5). In patients with HRD+ tumors excluding those with a tBRCA mutation, median OS with olaparib in combination with bevacizumab in the PAOLA-1 trial was not reached and 52.0 months for olaparib plus bevacizumab and placebo plus bevacizumab, respectively, with an HR of 0.71 (95% CI 0.45, 1.13). 5-year survival was 54.7% and 44.2% in olaparib plus

Summary	
	bevacizumab and bevacizumab plus placebo arms, respectively(6).
Type of evidence for the clinical evaluation	Anchored MAIC was used to compare rucaparib (ATHENA-MONO(7)) with niraparib (PRIMA(5)). Unanchored MAIC was used to compare rucaparib (ATHENA-MONO(7)) with olaparib in combination with bevacizumab (PAOLA-1(6)).
Most important efficacy endpoints (Difference/gain compared to comparator)	Adjusted HRs from the anchored MAIC analysis indicated a numerical advantage for rucaparib compared with niraparib for invPFS ([redacted]), PFS2 ([redacted]) and OS ([redacted]). [DCO 17MAY 2024] Adjusted HRs from the unanchored MAIC analysis indicated similarity between rucaparib and olaparib in combination with bevacizumab for invPFS ([redacted]), PFS2 ([redacted]) and OS ([redacted]). [DCO 17MAY 2024]
Most important serious adverse events for the intervention and comparator	Key safety outcomes included in the submission are treatment discontinuations due to adverse events and Grade 3-4 adverse events. In addition, there were key serious adverse events relevant for each of the treatments considered. For rucaparib, treatment discontinuations due to adverse events in the ATHENA-MONO trial were higher in the rucaparib arm vs. placebo (11.8% compared to 5.5%) (DCO 23 March 2022); the proportion of patients experiencing a grade 3 or 4 adverse event was higher in the rucaparib arm (60.5%) compared to the placebo arm (22.7%)(8). Adverse reactions leading to permanent discontinuation occurred in 15% of patients; with the most frequently reported being thrombocytopenia, nausea, anaemia, and fatigue/asthenia. The SmPC includes special warnings and precautions for use for haematological toxicity, MDS/AML, photosensitivity, gastrointestinal toxicities, intestinal obstruction, embryofoetal toxicity, and pregnancy/contraception.(1, 7) For niraparib, treatment discontinuations due to adverse events in the PRIMA study was higher in the niraparib arm vs. placebo (16.3% vs. 3.7); the proportion of patients experiencing a grade 3 or 4 adverse event was higher in the niraparib arm (73.8%) compared to the placebo arm (23.8%). The most common grade 3 or higher adverse events in the niraparib group were anaemia (31.0%), thrombocytopenia (28.7%), and neutropenia (12.8%). The SmPC includes special warnings and precautions for use for haematologic adverse reactions, MDS/AML, hypertension, including hypertensive crisis,

Summary	
	posterior reversible encephalopathy syndrome, pregnancy / contraception, and hepatic impairment.(5, 9) For olaparib in combination with bevacizumab, treatment discontinuations due to adverse events in the PAOLA-1 trial were higher in the olaparib plus bevacizumab arm vs. placebo plus bevacizumab (20% compared to 6%); the proportion of patients experiencing a grade 3 or 4 adverse event was higher in the olaparib plus bevacizumab arm (57%) compared to the placebo plus bevacizumab arm (51%). The most common serious adverse event that occurred at a higher incidence with olaparib plus bevacizumab than with placebo plus bevacizumab was anaemia (6% in the olaparib group and <1% in the placebo group). The SmPC includes special warnings and precautions for use for gastrointestinal perforations, fistulae, wound healing complications, hypertension, proteinuria, venous thromboembolism, haemorrhage, aneurysms and artery dissections, neutropenia and infections, hypersensitivity and osteonecrosis of the jaw.(10, 11)
Impact on health-related quality of life	Clinical documentation: There was no common HRQoL instruments included among studies of rucaparib, niraparib, or olaparib in combination with bevacizumab. ATHENA-MONO included EQ-5D-5L and FACT-O; PRIMA included FOSI, EORTC QLQ-C30, and EORTC QLQ-OV28; PAOLA-1 included EORTC QLQ-C30. Results across endpoints and studies indicated no difference in HRQoL between active and comparator arms. Health economic model: Since a cost comparison is submitted, the impact on health-related quality of life is not included in the analysis, but described for the included studies.
Type of economic analysis that is submitted	A cost-comparison, comparing the total treatment costs of rucaparib compared to niraparib.
Data sources used to model the clinical effects	No clinical effect was modelled since the efficacy is considered equivalent between rucaparib, niraparib, and olaparib in combination with bevacizumab.
Data sources used to model the health-related quality of life	N/A
Life years gained	N/A
QALYs gained	N/A
Incremental costs	Compared to niraparib: DKK [redacted]
ICER (DKK/QALY)	N/A

Summary	
Uncertainty associated with the ICER estimate	N/A
Number of eligible patients in Denmark	Incidence: Approximately [redacted] new patients per year
Budget impact (in year 5)	[redacted] DKK

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

3.1 The medical condition

The European Institute of Women's Health defines ovarian cancer as "cancer originating in the cells of the ovaries and fallopian tubes".(12) Over 90% of ovarian cancer cases in Denmark are epithelial; however, ovarian cancer is a heterogeneous disease with variation in histopathology, morphology and disease course.(4) The 2022 Dansk Gynaekologisk Cancer Gruppe (DGCG) guidelines on the epidemiology, hereditary factors, screening, disease course, staging and survival of ovarian cancer note that the aetiology of epithelial ovarian cancer is multifactorial, and most cases have no obvious cause.(4) While up to 40% of ovarian cancers are thought to be caused by genetics, the proportion of ovarian cancers with breast cancer gene (BRCA)1/2 mutations was only 5.8% in a study conducted in Denmark.(4)

People with ovarian cancer experience unpleasant or debilitating symptoms such as bloating, a feeling of heaviness and tension in the abdominals, decreased appetite, nausea, constipation, urinary frequency, fatigue, dyspnoea and deep venous thrombosis.(4, 13) In rare cases, patients may report dermatological, connective tissue, central nervous system or haematological symptoms.(4) Changes in global health, physical and physiological functioning, symptoms and health-related quality of life (HRQoL) can be further exacerbated in patients with disease progression following initial response to treatment.(14) Moreover, side effects of chemotherapy have a significant negative impact on HRQoL.(15, 16) Chemotherapy-associated toxicities can particularly reduce a patient's perception of health; in patients with relapsed and progressive disease, median utility values according to the EQ-5D® visual analogue scale can be as low as 0.17 in patients experiencing grade 3–4 toxicity.(17) Patients also experience distress caused by fear and anxiety of recurrence.(16)

Ovarian cancer is the 4th most common cause of cancer death in women in Denmark.(4) The prognosis of ovarian cancer is largely influenced by the stage of the disease at diagnosis, with 5-year survival in Denmark decreasing from ≥85% in patients with stage I cancer to ≤25% in patients with stage IV cancer based on the 2022 DGCG guidelines (Table 1).(4) Given that 75% to 80% of patients are diagnosed with locally advanced or advanced stage ovarian cancer (International Federation of Gynecology and Obstetrics [FIGO] stages II to IV), most patients with ovarian cancer have poor prognosis and an urgent need for treatment.(18) Factors such as advanced age, presence of ascites, low and undifferentiated tumour, macroscopic residual tumour after surgery, high post-operative CA-125 and poor performance status are also associated with worse survival outcomes.(4)

Table 1 Five-year survival for patients with epithelial ovarian cancer in Denmark(4, 19)

FIGO stage	Description	5-year survival
I	Tumour confined to ovaries or fallopian tube	85% to 86%
II	Tumour in one or both ovaries or fallopian tube with pelvic extension (below pelvic brim) or peritoneal cancer	65% to 68%
III	Tumour in one or both ovaries or fallopian tube or peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes	36% to 40%
IV	Distant metastasis excluding peritoneal metastases	20% to 25%

Abbreviation: FIGO = International Federation of Gynecology and Obstetrics

3.2 Patient population

The indication relevant for this submission is advanced ovarian, fallopian tube, or primary peritoneal cancer who are homologous recombination deficiency (HRD)-positive without BRCA mutation (also referred to as non-tBRCA loss of heterozygosity (LOH) high) in patients who have responded (complete or partial) to first-line platinum-based chemotherapy. A submission for the BRCA-mutated population has already been submitted to the Danish Medicines Council (DMC).

The subgroup included in this submission is appropriate for Danish clinical practice because the DGCG 2025 guideline recommendations for maintenance treatment in ovarian cancer separate patients by BRCA mutation and HRD status (see Section 0).(20) The 2022 guideline specifies that patients newly diagnosed with epithelial ovarian cancer should be offered BRCA testing for maintenance therapies.(4, 21) In addition, patients without BRCA mutation should be offered a HRD test to assess their suitability for a poly(ADP-ribose) polymerase (PARP) inhibitor (PARPi).(21) The DGCG recommendations

for BRCA and HRD testing are in line with the 2023 ESMO guidelines and the 2024 ESMO-ESGO-ESP consensus.(13, 22)

The DGCG estimates approximately 450 new cases of fallopian tube, ovarian and primary peritoneal cancer per year in Denmark.(4) This corresponds to an incidence rate of 15 per 100,000 women, which is the second highest in the world.(4) The lifetime risk of ovarian cancer in Denmark is approximately 2%.(4) Ovarian cancer is most common in postmenopausal women (80% of cases) and the median age of onset in Denmark is 63 years.(4) The incidence and prevalence of ovarian cancer over the last 5 years based on published data from the World Health Organization and NORDCAN is presented in Table 2.(23) The estimated number of patients eligible for treatment is presented in Table 3.

Table 2 Incidence and prevalence in the past 5 years

Year	2020	2021	2022	2023	2024
Incidence in Denmark(23)	0.015%	0.015%	0.015%	0.015%	0.015%
Prevalence in Denmark(23)	0.168%	0.168%	0.168%	0.168%	0.168%

Table 3 Estimated number of patients eligible for treatment*

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 (24)	100	100	100	100	101

*Calculated based on total female population in Denmark(25), multiplied by incidence of advanced ovarian cancer that are HRD+ without BRCA mutation(10, 26).

3.3 Current treatment options

Primary surgery is the standard of care in Denmark for advanced ovarian cancer, followed by adjuvant chemotherapy.(4) The 2024 and 2025 DGCG treatment guidelines recommend six cycles of combination chemotherapy with carboplatin and either paclitaxel or docetaxel after surgery.(18, 20) Alternatively, cisplatin can be used if carboplatin is not tolerated.(20) Between 60% and 80% of patients will achieve complete or partial response to surgery and chemotherapy.(4) However, approximately 80% will relapse within 2 years of completing chemotherapy in the absence of maintenance therapy.(4)

Thus, patients with FIGO stage III disease with macroscopic tumour tissue after primary surgery/interval debulking, all patients with stage IV disease, and inoperable patients, should be offered maintenance therapy, no earlier than 4 weeks after any surgery.(20)

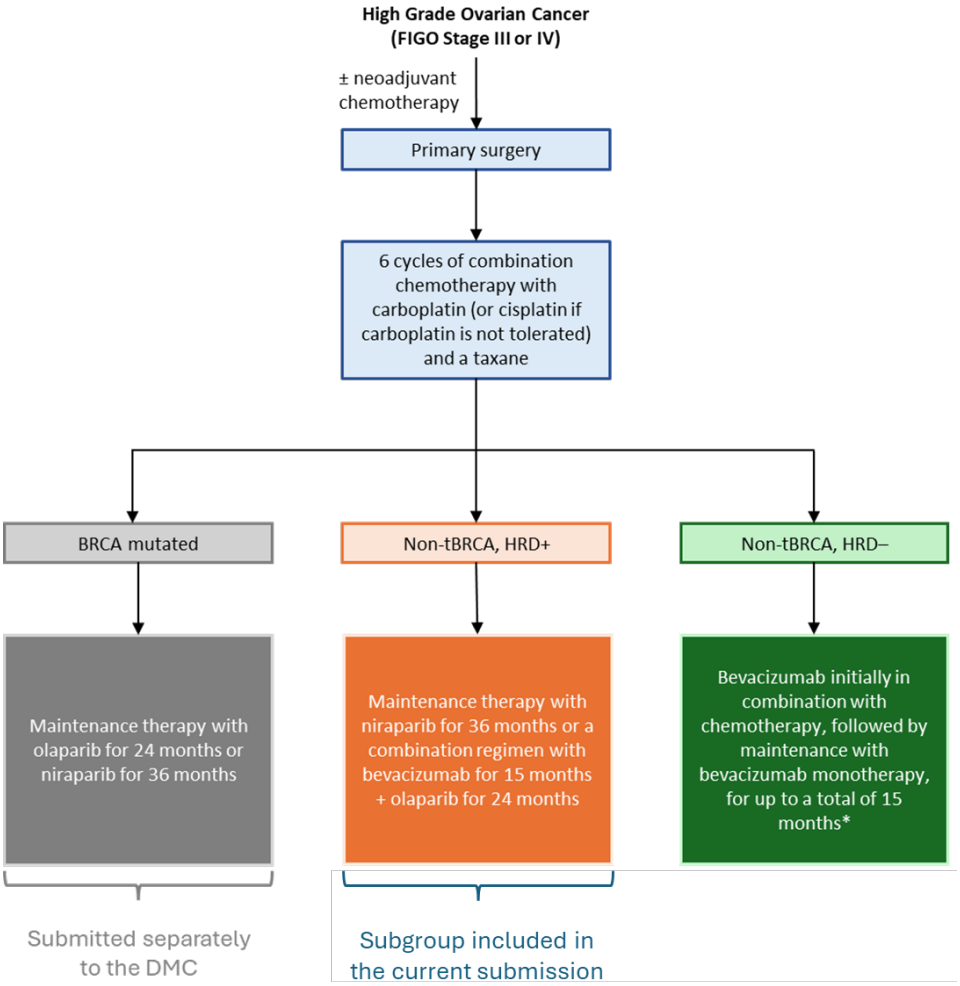
Treatment and maintenance therapy options for patients with newly diagnosed advanced ovarian cancer in Denmark are summarised in Figure 1.(20) First-line (1L) maintenance therapy recommendations vary with BRCA mutation status and HRD status(20):

- Patients with BRCA mutation should receive either 24 months of olaparib or 36 months of niraparib
- Patients who are tumour tissue BRCA mutation-negative (non-tBRCA) and HRD+ should receive either 36 months of niraparib or a combination regimen with 15 months of bevacizumab plus 24 months of Olaparib
- Patients who are non-tBRCA, HRD– should receive bevacizumab initially in combination with chemotherapy, followed by maintenance treatment with bevacizumab as monotherapy, for a total of 15 months

In the non-tBRCA, HRD- population the DGCG 2025 guideline also suggests 36 months of niraparib despite the DMC not recommending niraparib for this indication because of a lack of survival benefit and adverse events (AEs).(20) As of February 2025, niraparib and olaparib plus bevacizumab are the only 1L maintenance therapies that have been recommended by the DMC for non-tBRCA HRD+ patients:

- Niraparib was recommended in 2021 for patients with ovarian cancer with BRCA mutation or patients who are HRD+ (including patients who are HRD+ but do not have BRCA mutation). However, niraparib is not recommended for patients who do not have a BRCA mutation and are HRD–.(2)
- Olaparib plus bevacizumab was recommended in 2024 for patients with ovarian cancer who are HRD+ without BRCA mutation.(3)

Figure 1 Treatment and maintenance therapy options for patients with newly diagnosed advanced ovarian cancer in Denmark(20)



Abbreviations: BRCA = breast cancer gene; DMC = Danish Medicines Council; FIGO = International Federation of Gynecology and Obstetrics; HRD = homologous recombination deficiency; tBRCA = tumour tissue mutation in breast cancer gene

* The DGCG 2025 guideline also suggests 36 months of niraparib for patients with who are non-tBRCA, HRD–; however, this is not recommended by the DMC

3.4 The intervention

The intervention in this submission is rucaparib. Rucaparib is an inhibitor of PARP enzymes indicated as monotherapy for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of 1L platinum-based chemotherapy.(1) The population relevant for this assessment is non-tBRCA HRD+ patient. An overview of the intervention is presented in Table 4.

Table 4 Overview of rucaparib

Overview of intervention	
Indication relevant for the assessment	First-line maintenance treatment of advanced cancer of the ovaries, fallopian tubes or primary cancer of the peritoneum for patients with epithelial cell high grade carcinoma and homologous recombination defect (HRD+), but without BRCA1/2 mutation.
ATMP	N/A
Method of administration	Oral
Dosing	Rucaparib is provided as a film-coated tablet. The recommended dose of rucaparib is 600 mg (two 300 mg tablets) taken orally twice daily with or without food (1,200 mg total daily dose).(1) Interruption of treatment or dose reduction (600 mg to 500 mg [two 250 mg tablets] to 400 mg [two 200 mg tablets] to 300 mg [one 300 mg tablet]) can be considered for AE management.(1)
Dosing in the health economic model (including relative dose intensity)	1200mg daily oral dose (two 300mg tables twice daily). A mean RDI of 82% is used in the base-case analysis, calculated in the ATHENA-MONO trial (27). Mean RDI was defined as the actual total dose over time divided by the protocol-specified starting dose of 600 mg BID.
Should the medicine be administered with other medicines?	No
Treatment duration / criteria for end of treatment	Patients can continue treatment until disease progression, unacceptable toxicity or completion of 2 years treatment.(1) In the cost-comparison analysis, the treatment duration was based on the extrapolation of time-to-treatment discontinuation. In the ATHENA-MONO study, a median of [redacted] months was reported(28).
Necessary monitoring, both during administration and during the treatment period	Weekly blood counts are not advised for patients treated with rucaparib. Complete blood count testing prior to starting treatment with rucaparib, and monthly thereafter, is advised. No starting dose adjustment is required in patients with mild or moderate renal impairment.(1)
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	N/A

Overview of intervention	
Package size(s)	Rucaparib is supplied in plastic bottles, each containing 60 film-coated tablets (200 mg, 250 mg or 300 mg).(1)

Abbreviations: 1L = first-line; AE = adverse event; BRCA = breast cancer gene; DMC = Danish Medicines Council; HRD = homologous recombination deficiency; N/A = not applicable; SE = standard error

3.4.1 Description of ATMP

N/A

3.4.2 The intervention in relation to Danish clinical practice

Rucaparib represents a new, flexible mode of PARP inhibition for 1L maintenance therapy that will allow physicians to manage ovarian cancer in an individualised manner, irrespective of patients' BRCA status.(1, 7) Rucaparib is effective, well-tolerated and has a safety profile that differs from that of other PARP inhibitor maintenance treatments and bevacizumab monotherapy.(1, 7, 9, 11, 29, 30) In The ATHENA-MONO trial, rucaparib showed significantly improved PFS vs. placebo (DCO 23 March 2022; inv-PFS for ITT population: 20.2 vs 9.2 months; HR 0.52 (95% CI: 0.40 – 0.68)(7)) regardless of HRD test status and demonstrated clear benefit in a patients with advanced OC (including patients with stage III disease and patients without residual disease prior to chemotherapy).(7, 31) The availability of four dose reduction steps in the ATHENA-MONO study offers additional flexibility for managing side effects with rucaparib(7).

Within the current Danish treatment pathway, rucaparib would provide a PARP inhibitor maintenance option independent of biomarker status and with a distinct clinical profile. Clinicians would thereby be afforded the option to focus on a patient-specific maintenance regimen via the most suitable PARP inhibitor. Based on the clinical evidence presented in Section 6.1.4 and the safety evidence summarised in Section 9.1, rucaparib is expected to address an important unmet medical need in current clinical practice. Rucaparib may further advance the incorporation of PARP inhibitor maintenance treatment within the standard of care for people with platinum-sensitive ovarian cancer in the 1L setting and improve the currently poor prognosis for advanced stage ovarian cancer in Denmark.

3.4.2.1 Shortcomings with current options for maintenance therapy after response to 1L platinum-based chemotherapy

Observations that patients with lower body weight (<77 kg) or lower baseline platelet count (<150,000/µL) treated with niraparib may be at higher risk of grade ≥3 thrombocytopenia led to the introduction of the 200 mg once daily dose for these patients.(9) However, the European Medicines Agency (EMA) assessment report for niraparib noted in the conclusion that 'it cannot be affirmably stated that there is no loss of efficacy with the 200 mg starting dose [compared with the 300 mg starting dose]'.(32) This EMA noted that 'the efficacy seems to not be fully maintained with the 200 mg

starting dose' for the overall population and the HRD positive subgroup and 'the 200 mg dose seems to be of lower efficacy compared to 300 mg' in the HRD negative subgroup.(32) Maintenance therapy with niraparib is also associated with substantial monitoring requirements.(9) Specifically, complete blood counts must be monitored weekly during the first month of treatment and blood pressure is monitored weekly for the first 2 months.(9) Blood pressure should be monitored at least weekly for two months, monitored monthly afterwards for the first year and periodically thereafter during treatment with niraparib(9).

1L maintenance treatments involving bevacizumab have been associated with AE-related treatment discontinuation rates as high as 20%.(10, 11, 29) Moreover, bevacizumab must be administered intravenously once every 3 weeks under the supervision of a physician.(33) Published data on patient-reported preferences regarding mode of administration for cancer treatments suggests most patients prefer oral administration over intravenous administration for reasons such as 'convenience', 'ability to receive treatment at home' and 'less impact on daily life and family'.(34)

Recent evidence based on a retrospective pooled analysis of large randomised controlled trials (RCTs) of bevacizumab therapy published by Takamatsu et al. (2023) suggests the progression-free survival (PFS) benefit of bevacizumab maintenance therapy may be limited.(35) Restricted mean survival time analysis found PFS to be significantly better in patients treated with bevacizumab maintenance before treatment discontinuation in ICON-7 (induction carboplatin + paclitaxel + bevacizumab followed by maintenance bevacizumab) but significantly worse after treatment discontinuation regardless of HRD status (all $p \leq 0.04$).(35) A similar pattern was also observed with the GOG-0218 trial (induction carboplatin + paclitaxel + bevacizumab followed by maintenance bevacizumab), suggesting that bevacizumab maintenance therapy may be less effective in patients with longer prognosis (i.e., those with expected survival of >1 year) who may be negatively impacted by the progression of disease (i.e. 'rebound effect').(35) The authors noted the existing evidence suggests bevacizumab may block the growth of cancer cells (cytostatic) without killing cancer cells (cytotoxic).(35) Furthermore, recently published results from the BOOST study, which assessed the efficacy of bevacizumab in combination with 1L chemotherapy for 30 months vs. 15 months, found no additional PFS or overall survival (OS) benefit associated with longer bevacizumab treatment duration.(36)

While common TEAEs align across the drug class, differences in the safety profiles of PARP inhibitor maintenance treatments are noted.(1, 9, 29) Due to the consistent and manageable safety profile of rucaparib,(30) no starting dose adjustment is required for elderly patients (≥65 years of age) or for patients with mild or moderate hepatic or renal impairment.(1) Moreover, potentially burdensome weekly blood counts are not advised for patients treated with rucaparib; instead, complete blood count should be tested prior to starting treatment with rucaparib, and monthly thereafter.(1) In case of AEs, a flexible 3-step dose-reduction can be applied, whereby a 1 month pack of 60 tablets allows for flexible dosing adaptation.(1) A summary of cautions and serious adverse events (SAEs) associated with niraparib, olaparib and bevacizumab is presented in Table 5 (18).

Table 5 Overview of cautions and serious adverse events associated with 1L maintenance therapy options for ovarian cancer in Denmark(18)

Treatment	Cautions and serious adverse events listed in the DGCG guidelines
Niraparib	The most frequent (>10%) serious adverse reactions to niraparib were blood and lymphatic system (anaemia, leukopenia, neutropenia, thrombocytopenia), gastrointestinal tract (abdominal pain, diarrhoea, dyspepsia, nausea, constipation, vomiting, taste disturbances), fatigue, weakness, decreased appetite, arthralgia, back pain, urinary tract infection, nervous system (dizziness, headache), respiratory (dyspnoea, cough, nasopharyngitis), and hypertension. The most common side effects such as fatigue and nausea typically disappear after the first 3 months of treatment.
Olaparib	The most frequent (>10%) serious adverse reactions to olaparib were blood and lymphatic system (anaemia, leukopenia, neutropenia, thrombocytopenia, creatinine elevation), gastrointestinal tract (diarrhoea, dyspepsia, nausea, vomiting, taste disturbances), fatigue, decreased appetite, nervous system (dizziness, headache) and respiratory (dyspnoea, cough). Late development of haematological toxicity has been observed due to multi-year treatments. In the case of effects on the bone marrow with risk of MDS, a haematologist must be consulted and possibly additional bone marrow examination performed. The most common side effects such as fatigue and nausea typically disappear after the first 3 months of treatment.
Bevacizumab	The most frequent (>10%) serious adverse reactions to bevacizumab were abdominal pain, bleeding, poor wound healing, proteinuria, arthralgia, dermatitis, hypertension and thromboembolism. Caution is advised under the following circumstances: • Inflammatory bowel diseases due to risk of gastrointestinal and gallbladder perforation. Consider imaging to assess possible intestinal ingrowth prior to initiation of treatment. • Use of VEGF inhibitors may promote the formation of aneurysms and/or arterial dissections. • The risk should be carefully considered for patients with risk factors (e.g., hypertension or previous aneurysm). • Blood pressure must be well controlled before starting treatment and must be monitored during treatment. • Heart disease, and consideration of treatment indication, if currently on treatment due to bleeding risk. • Increased risk of developing fistulas, especially with previous pelvic radiation therapy.

Abbreviations: 1L = first line; DGCG = Dansk Gynaekologisk Cancer Gruppe; MDS = myelodysplastic syndrome; VEGF = vascular endothelial growth factor

3.5 Choice of comparator(s)

1L maintenance therapy options for patients with ovarian cancer in the non-tBRCA, HRD+ population are niraparib or olaparib plus bevacizumab.(2, 3, 20) Both therapies are recommended by the DMC and in the DGCG 2025 treatment guidelines.(2, 3, 20)

Based on drug utilisation data in ovarian cancer in Denmark, the majority of patients (63%) with non-tBRCA, LOH+ aOC are not eligible for bevacizumab.(24) Therefore, niraparib may be considered the closest comparator to rucaparib in this patient population. In the recommendation for olaparib plus bevacizumab, the DMC noted that olaparib plus bevacizumab is considered clinically equivalent to niraparib for 1L maintenance treatment of patients with non-tBRCA, HRD+ ovarian cancer.(3)

Table 6 Overview of niraparib

Overview of comparator	
Generic name	Niraparib
ATC code	L01XK02
Mechanism of action	PARP inhibitor(9)
Method of administration	Oral(9)
Dosing	The recommended starting dose is 200 mg (two 100 mg capsules), taken together once a day, with or without food. For patients who weigh ≥ 77 kg and have platelet count ≥150,000/µL before starting treatment, the recommended starting dose is 300 mg (three 100 mg capsules), taken together once a day, with or without food. The dose may be reduced to 100 mg to manage adverse reactions.(9)
Dosing in the health economic model (including relative dose intensity)	200mg or 300mg daily dose (two or three 100mg capsules). An RDI of 62.6% was used in the base-case analysis, equating to a median dose of 181.3mg/day.(37)
Should the medicine be administered with other medicines?	No
Treatment duration/ criteria for end of treatment	It is recommended that treatment should be continued until disease progression or toxicity in the SmPC.(9) The DGCG guidelines recommend 36 months of treatment with niraparib.(20) In the cost-comparison analysis, due to lack of data on time-to-treatment discontinuation from the PRIMA study, median time-to-treatment discontinuation was assumed equal to those extrapolated for rucaparib in the ATHENA-MONO study in line with the assumption of comparable efficacy between rucaparib and niraparib.

Overview of comparator	
Need for diagnostics or other tests (i.e. companion diagnostics)	Yes. The DMC recommendation for niraparib is restricted to patients with BRCA mutation or HRD+.(2) Thus patients should receive BRCA and HRD testing.
Package size(s)	Niraparib is supplied in cartons of 84 and 56 film-coated tablets.(9)

Abbreviations: BRCA = breast cancer gene; DGCG = Dansk Gynaekologisk Cancer Gruppe; DMC = Danish Medicines Council; HRD = homologous recombination deficiency; PARP = poly(ADP-ribose) polymerase; SmPC = summary of product characteristics

Table 7 Overview of olaparib

Overview of comparator	
Generic name	Olaparib
ATC code	L01XK01
Mechanism of action	PARP inhibitor(29)
Method of administration	Oral(29)
Dosing	Olaparib is recommended at a dose of 300 mg (2 × 150 mg tablets) taken twice daily with or without food, equivalent to a total daily dose of 600 mg. The 100 mg tablet is available for dose reductions. Dose adjustments may be required for renal impairment or adverse reactions.(29)
Dosing in the health economic model (including relative dose intensity)	600mg daily dose (2 times 150mg tables daily). An RDI of 97.5% for olaparib plus bevacizumab was used for sensitivity analyses (NICE TA693 Assessment of olaparib with bevacizumab for maintenance treatment of advanced ovarian cancer Committee Papers; p87(38)).
Should the medicine be administered with other medicines?	Yes, in combination with bevacizumab in non-tBRCA HRD+ patients.
Treatment duration/ criteria for end of treatment	It is recommended that treatment should be continued until disease progression or toxicity in the SmPC.(9) The DGCG guidelines recommend 24 months of treatment with olaparib.(20)
Need for diagnostics or other tests (i.e. companion diagnostics)	Yes. The DMC recommendation for olaparib plus bevacizumab is restricted to patients with BRCA mutation or HRD+.(2) Thus patients should receive BRCA and HRD testing.
Package size(s)	Olaparib is supplied in cartons of 56 film-coated tablets of 100mg or 150mg dosage.(29)

Abbreviations: BRCA = breast cancer gene; DGCG = Dansk Gynaekologisk Cancer Gruppe; DMC = Danish Medicines Council; HRD = homologous recombination deficiency; PARP = poly(ADP-ribose) polymerase; SmPC = summary of product characteristics

Table 8 Overview of bevacizumab

Overview of comparator	
Generic name	Bevacizumab
ATC code	L01XC07
Mechanism of action	Monoclonal antibody that binds to VEGF to inhibit tumour growth.(11)
Method of administration	Intravenous
Dosing	The recommended dose of bevacizumab is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.(11)
Dosing in the health economic model (including relative dose intensity)	1,012.35mg average dose (15mg per kg for 67.49kg average weight, every 3 weeks). An RDI of 97.5% for olaparib plus bevacizumab was used for sensitivity analyses (NICE TA693 Assessment of olaparib with bevacizumab for maintenance treatment of advanced ovarian cancer Committee Papers; p87(38)).
Should the medicine be administered with other medicines?	Yes, in combination with bevacizumab in non-tBRCA HRA+ patients.
Treatment duration/ criteria for end of treatment	Until disease progression or for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier.(11, 20)
Need for diagnostics or other tests (i.e. companion diagnostics)	Yes. Olaparib in combination with bevacizumab as a maintenance therapy is recommended for patients with HRD+ and no BRCA mutation.(2) Thus patients should receive BRCA mutation and HRD testing.
Package size(s)	Each pack of bevacizumab contains one vial (4 ml solution containing 100 mg of bevacizumab or 16 ml solution containing 400 mg of bevacizumab).(11)

Abbreviations: BRCA = breast cancer gene; DGCG = Dansk Gynaekologisk Cancer Gruppe; DMC = Danish Medicines Council; HRD = homologous recombination deficiency; NICE = National Institute for Health and Care Excellence; VEGFR = vascular endothelial growth factor

3.6 Cost-effectiveness of the comparator(s)

Both niraparib and olaparib in combination with bevacizumab has been evaluated and recommended by the DMC for the treatment of first-line maintenance treatment of advanced cancer of the ovaries, fallopian tubes or primary cancer of the peritoneum for patients with epithelial cell high-grade carcinoma and HRD+, but without BRCA1/2 mutation. (2, 3)

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

In the absence of direct comparative studies, an indirect treatment comparison (ITC) via a matched adjusted indirect comparison (MAIC) was conducted comparing rucaparib to niraparib and rucaparib to olaparib in combination with bevacizumab.

The relevant efficacy outcomes included in this comparison are investigator-assessed progression-free survival (invPFS), OS, and progression-free survival to second progression (PFS2) (Table 9). Safety and HRQoL outcomes are assessed in Section 9 and Section 0, respectively.

Table 9 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
invPFS [ATHENA-MONO(7, 27, 39, 40), PRIMA (7, 41), PAOLA-1 (6, 10)	Data used in the analysis was based on DCO 17 May 2024 (median duration of follow-up 4 years)	invPFS is defined as time from randomisation to disease progression +1 day, as determined by RECIST v1.1 criteria or death due to any cause, whichever occurred first.	Non-parametric survival analysis (Kaplan-Meier, unstratified HR calculation [including log-rank test]) and parametric survival analysis.
OS [ATHENA-MONO(27, 40, 42), PRIMA (7, 41), PAOLA-1 (6, 10)	Data used in the analysis was based on DCO 9 March 2023 (median duration of follow-up 26 months + approximately 1 year follow-up)	OS is defined as the time from randomisation to date of death due to any cause.	Non-parametric survival analysis (Kaplan-Meier, unstratified HR calculation [including log-rank test]) and parametric survival analysis.
PFS2 [ATHENA-MONO(42-44),	Data used in the analysis was based on	PFS2 is defined as the time from randomisation to the second event of disease	Non-parametric survival analysis (Kaplan-Meier, unstratified HR calculation

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
PRIMA (7, 41), PAOLA-1 (6, 10)	DCO 17 May 2024 (median duration of follow-up 4 years)	progression as assessed by the investigator or death due to any cause.	[including log-rank test]) and parametric survival analysis.

Abbreviations: DCO = data cut-off; invPFS = investigator-assessed progression-free survival; OS = overall survival; PFS2 = progression-free survival to second progression; RECIST = Response Evaluation Criteria In Solid Tumours; TTD = time to treatment discontinuation
*Note: the maximum treatment duration with rucaparib is 2 years.(1)

Validity of outcomes

OS and PFS were included as key outcomes in the niraparib(2) and olaparib in combination with bevacizumab assessment(3) and were deemed appropriate by the DMC. Relevant HRQoL outcomes, such as EQ-5D-5L, FOSI, FACT-O, EORTC-QLQ-C30, and QLQ-OV28 were not consistently collected across studies and were reported where available. HRQoL outcomes could not be compared indirectly.

4. Health economic analysis

Rucaparib, niraparib, and olaparib are PARP inhibitors with similar mechanism of action. In a recent update of DMC's drug recommendation and treatment guidelines regarding maintenance of advanced ovarian cancer in patients with a BRCA mutation(45), rucaparib, niraparib, and olaparib were deemed to have a comparable efficacy and safety profile.

4.1 Model structure

The health economic model is based on a simple cost comparison of the treatment costs of rucaparib and niraparib accumulated over a 4-year time horizon, to capture the costs over the expected duration of treatment across all relevant treatments as well as subsequent therapy.

4.2 Model features

Table 10 presents a summary of the model features included in the cost comparison.

Table 10 Features of the economic model

Model features	Description	Justification
Patient population	First-line maintenance treatment of advanced cancer of the ovaries, fallopian tubes or primary cancer of the peritoneum for patients with	Based on reimbursement population used in other assessments(2, 46).

Model features	Description	Justification
	epithelial cell high-grade carcinoma and homologous recombination defect (HRD+), but without BRCA1/2 mutation.	
Perspective	N/A	N/A
Time horizon	4 years	To capture the expected treatment duration across all relevant treatments and subsequent therapy.
Cycle length	Monthly	in line with rucaparib and niraparib administration and monitoring cycles
Half-cycle correction	Applied by calculating state occupancy at the half-point in between two cycles	In line with DMC guidance
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 % for all years
Intervention	Rucaparib	N/A
Comparator(s)	Niraparib	Reimbursed alternative in Denmark.
Outcomes	Overall cost	Total treatment, patient time, transport, monitoring, and subsequent therapy cost calculated over a period of 4 years.

5. Overview of literature

5.1 Literature used for the clinical assessment

A systematic literature review was conducted to identify relevant efficacy and safety information in patients receiving maintenance treatment following 1L systemic therapy. The methods of this literature review are summarised in Appendix H. The literature used in the clinical assessment is summarised in Table 11.

Table 11 Relevant literature included in the assessment of efficacy and safety [sample text in table for full paper, data on file and conference abstract]

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*
Monk BJ, Parkinson C, Lim MC, et al. A Randomized, Phase III Trial to Evaluate Rucaparib Monotherapy as Maintenance Treatment in Patients With Newly Diagnosed Ovarian Cancer (ATHENA-MONO/GOG-3020/ENGOT-ov45). Journal of Clinical Oncology : official journal of the American Society of Clinical Oncology. Dec 1 2022;40(34):3952-3964. doi:10.1200/jco.22.01003(7) Fujiwara K, Kristeleit R, Ghamande S, et al. Rucaparib maintenance treatment in patients (pts) with newly diagnosed ovarian cancer (OC): defining benefit according to disease risk subgroups within the phase III ATHENA-MONO study. Annals of oncology. 1505;33:S1505-S1506. doi:10.1016/j.annonc.2022.10.214.(47) Kristeleit R, Ghamande S, Lim M, et al. 527MO Rucaparib maintenance treatment in patients (pts) with newly diagnosed ovarian cancer (OC): defining benefit according to disease risk subgroups within the phase 3 ATHENA-MONO study. Annals of oncology. 2022;33:S786-S787. doi:10.1016/j.annonc.2022.07.655.(48) Oaknin A, Kristeleit R, Mahdi H, et al. Patients with Newly Diagnosed Ovarian Cancer Treated with Maintenance Rucaparib: Exploratory Biomarker Analysis from the Phase 3 ATHENA-MONO Study (Gog-3020/ Engot-Ov45; Nct03522246). International journal of gynecological cancer. 2022;32:2022-10. doi:10.1136/ijgc-2022-esgo.1018.(49) O'Malley D, Christopoulou A, Lim M, et al. Efficacy Analysis by Disease Risk Subgroup for the Phase 3 ATHENA-MONO Study (GOG- 3020/ENGOT-Ov45) Evaluating Rucaparib Maintenance Treatment in Patients with Newly Diagnosed Ovarian Cancer. International journal of gynecological cancer. 2022;32:2022-09. doi:10.1136/ijgc-2022-igcs.28.(50) O'Malley D, Monk B, Lim M, et al. Final safety results from ATHENA-MONO (GOG-3020/ENGOT-ov45), a randomized, placebo-controlled, double-blind, phase 3 trial evaluating rucaparib monotherapy as	ATHENA-MONO	NCT03522246	Start: October 2018 Completion: September 2020	Rucaparib monotherapy vs. placebo for maintenance treatment following response to first-line platinum-based chemotherapy in ovarian cancer.

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*
maintenance treatment in patients with newly diagnosed ovarian cancer. Journal of Clinical Oncology. 2024;42(16).(8) Kristeleit R, O'Malley D, Lim MC, McNeish I, Herzog TJ, Wilson M, Fehm TN, Coleman RL, Van Gorp T, Oza AM, Mikheeva O. 49MO Updated progression-free survival (PFS) in patients (pts) with newly diagnosed advanced ovarian cancer (OC) treated with rucaparib (RUC) in ATHENA-MONO. ESMO open. 2024 Jun 1;9.(51) Clovis Oncology INC. ATHENA-MONO Interim clinical study report [CONFIDENTIAL], 2022 (27) *Kristeleit R, O'Malley D, Lim MC, et al. Interim post-progression data and updated survival in patients with newly diagnosed advanced ovarian cancer in ATHENA-MONO. Gynecologic Oncology. 2024(40) *Ghamande S, Miller R, Solovyeva E, et al. ATHENA-MONO Post-Progression Survival Data Update In Patients With Newly Diagnosed Advanced Ovarian Cancer. International Journal of Gynecological Cancer. 2025(44) *Lorusso D, Kristeleit R, O'Malley D, et al. RUCAPARIB MAINTENANCE TREATMENT IN PATIENTS (PTS) WITH NEWLY DIAGNOSED OVARIAN CANCER (OC): DEFINING BENEFIT ACCORDING TO DISEASE RISK SUBGROUPS WITHIN THE PHASE 3 ATHENA-MONO STUDY. International Journal of Gynecological Cancer. 2024(52) *Kristeleit, R. S., Ghamande, S., Lisyanskaya, A. et al. Rucaparib maintenance for newly diagnosed advanced ovarian cancer: interim overall survival, progression-free survival, and safety at 5 years of follow-up from the phase III ATHENA-MONO/GOG-3020/ENGOT-ov45. Annals of Oncology. 2025(53) *New publications for rucaparib after SLR search was conducted				

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*
González-Martín A, Pothuri B, Vergote I, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. New England Journal of Medicine. 2019;381(25):2391-2402. doi:10.1056/NEJMoa1910962(54) Barretina-Ginesta M, Monk B, Han S, et al. Quality-adjusted time without symptoms of disease or toxicity and quality-adjusted progression-free survival with niraparib maintenance in first-line ovarian cancer in the PRIMA trial. Therapeutic Advances in Medical Oncology. 2022;14:17588359221126149. doi:10.1177/17588359221126149.(55) Chase D, Marin M, Backes F, et al. Impact of disease progression on health-related quality of life of advanced ovarian cancer patients - Pooled analysis from the PRIMA trial. Gynecologic Oncology. 2022;166(3):494-502. doi:10.1016/j.ygyno.2022.06.028.(14) Chase D, Romeo Marin M, Backes F, et al. Impact of disease progression on healthrelated quality of life of advanced ovarian cancer (AOC) patients-pooled analysis from the prima trial. International journal of gynecological cancer. 2021;Vol.31(SUPPL 1):A284p. doi:10.1136/ijgc-2021-esgo.494.(56) Gonzalez Martin A, Pothuri B, Vergote I, et al. PRIMA/ENGOT-OV26/GOG-3012 study: updated long-term PFS and safety. Annals of oncology. 2022;33:2022-09. doi:10.1016/j.annonc.2022.07.658.(57) Gonzalez Martin A, Pothuri B, Vergote I, et al. 33O PRIMA/ENGOT-OV26/GOG-3012 study: long-term conditional PFS. ESMO open. 2023;8(1). doi:10.1016/j.esmoop.2023.100813.(58) Mirza M, Gonzalez-Martin A, Graybill W, et al. Prospective evaluation of the tolerability and efficacy of niraparib dosing based on baseline body weight and platelet count: Results from the PRIMA/ENGOT-OV26/GOG-3012 trial. Cancer. 2023;129(12):1846-1855. doi:10.1002/cncr.34706.(37)	PRIMA	NCT02655016	Start: July 2016 Completion: May 2019	Niraparib vs placebo for patients with newly diagnosed advanced ovarian cancer receiving maintenance therapy

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*
O'Cearbbhaill R, Perez-Fidalgo J, Monk B, et al. Efficacy of niraparib by timing of surgery and residual disease: a Post Hoc analysis of patients in the PRIMA/ENGOT-OV26/GOG-3012 Study. Tumori. 2021;Vol.107(2 SUPPL):36p. doi:10.1177/03008916211041664.(59) O'Cearbhaill R, Grabowski J, Perez-Fidalgo J, et al. Efficacy of niraparib by timing of surgery and residual disease: a post-hoc analysis of patients in the PRIMA/ENGOT-OV26/ GOG-3012 study. Oncology research and treatment. 2022;45:120-121. doi:10.1159/000521004.(60) Herzog TJ, Wahab SA, Mirza MR, et al. Optimizing disease progression assessment using blinded central independent review and comparing it with investigator assessment in the PRIMA/ENGOT-ov26/GOG-3012 trial: challenges and solutions. Int J Gynecol Cancer 2023;33:1733–1742(61) Gonzalez-Martin A, Pothuri B, Barretina Ginesta M, et al. LBA29 Final overall survival (OS) in patients (pts) with newly diagnosed advanced ovarian cancer (aOC) treated with niraparib (nir) first-line (1L) maintenance: Results from PRIMA/ENGOT-OV26/GOG-3012. Annals of Oncology. 2024;35(Supplement 2):S1222-S1223. doi:10.1016/j.annonc.2024.08.2268.(62) Gonzalez-Martin A, Pothuri B, Vergote I, et al. Progression-free survival and safety at 3.5 years of follow-up: results from the randomized phase 3 PRIMA/ENGOT-OV26/GOG-3012 trial of niraparib maintenance treatment in patients with newly diagnosed ovarian cancer - a plain language summary. Future oncology (London, England). 2024;:1-14. doi:10.2217/fon-2023-0782.(41) Monk B, Barretina-Ginesta M, Pothuri B, et al. Niraparib first-line maintenance therapy in patients with newly diagnosed advanced ovarian cancer: final overall survival results from the PRIMA/ENGOT-OV26/GOG-3012 trial. Annals of oncology : official journal of the European Society for Medical Oncology. 2024;doi:10.1016/j.annonc.2024.08.2241.(5)				

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*
Pothuri B, Han S, Chase D, et al. Health-related quality of life in patients with newly diagnosed advanced ovarian cancer treated with niraparib vs placebo: Results from the phase 3 randomized PRIMA/ENGOT-OV26/GOG-3012 trial. Gynecologic oncology. 2024;184:168-177. doi:10.1016/j.ygyno.2024.01.021.(63) Valabrega G, Pothuri B, Oaknin A, et al. Efficacy and safety of niraparib in patients aged 65 years and older with advanced ovarian cancer: Results from the PRIMA/ENGOT-OV26/GOG-3012 trial. Gynecologic oncology. 2024;187:128-138. doi:10.1016/j.ygyno.2024.03.009.(64) Vulsteke C, Chambers S, Perez M, et al. Tolerability of the niraparib individualized starting dose in the PRIMA/ENGOT-OV26/GOG-3012 trial of niraparib first-line maintenance therapy. European journal of cancer (Oxford, England : 1990). 2024;208:114157. doi:10.1016/j.ejca.2024.114157.(65) Braicu EI, Pothuri B, Pérez-Fidalgo JA, et al364 Efficacy of niraparib therapy in patients with newly diagnosed advanced ovarian cancer by brcawt status: prima/ENGOT-OV26/GOG-3012 studyInternational Journal of Gynecologic Cancer 2020;30:A70-A71.(66) Vulsteke C, Chambers SK, Rubio Pérez MJ, et al#556 Tolerability of the niraparib individualised starting dose in the PRIMA/ENGOT-OV26/GOG-3012 trial of niraparib first-line maintenance therapyInternational Journal of Gynecologic Cancer 2024;34:A580-A581(67) Pothuri, B., Valabrega, G., Oaknin, A., Graybill, W., Sánchez, A. B., McCormick, C., ... & González-Martín, A. (2024). Examining health-related quality of life outcomes among older patients with advanced ovarian cancer treated with niraparib first-line maintenance therapy in context with efficacy and safety findings: Results from the PRIMA/ENGOT-OV26/GOG-3012 trial. Gynecologic Oncology, 190, S295-S296.(68)				
Ray-Coquard I, Pautier P, Pignata S, et al. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. The New England journal of medicine. Dec 19 2019;381(25):2416-2428. doi:10.1056/NEJMoa1911361(10)	PAOLA-1	NCT02477644	July 2015 - September, 2017	Olaparib in combination with bevacizumab vs bevacizumab in

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*
Fujiwara K, Fujiwara H, Yoshida H, et al. Olaparib plus bevacizumab as maintenance therapy in patients with newly diagnosed, advanced ovarian cancer: Japan subset from the PAOLA-1/ENGOT-ov25 trial. Journal of Gynecologic Oncology. 2021;32(5):e82. doi:10.3802/jgo.2021.32.e82.(69) Gonzalez-Martin A, Desauw C, Heitz F, et al. Maintenance olaparib plus bevacizumab in patients with newly diagnosed advanced high-grade ovarian cancer: Main analysis of second progression-free survival in the phase III PAOLA-1/ENGOT-ov25 trial. European Journal of Cancer. 2022;174:221-231. doi:10.1016/j.ejca.2022.07.022.(70) Gonzalez Martin A, Medioni J, Harter P, et al. 36MO Maintenance olaparib plus bevacizumab (bev) in patients (pts) with newly diagnosed advanced ovarian cancer (OC): 5-year (y) progression-free survival (PFS) by molecular subgroup in the PAOLA-1/ENGOT-ov25 trial. ESMO open. 2023;8(1):2023-02. doi:10.1016/j.esmoop.2023.100816.(71) Harter P, Mouret-Reynier M, Pignata S, et al. Efficacy of maintenance olaparib plus bevacizumab according to clinical risk in patients with newly diagnosed, advanced ovarian cancer in the phase III PAOLA-1/ENGOT-ov25 trial. Gynecologic Oncology. 2022;164(2):254-264. doi:10.1016/j.ygyno.2021.12.016.(72) Hietanen S, Pautier P, Harter P, et al. RECIST/CA-125 progression-free survival and the role of CA-125 surveillance in the phase III PAOLA-1/ENGOT-ov25 trial evaluating maintenance olaparib plus bevacizumab in patients with newly diagnosed advanced high-grade ovarian carcinoma. Gynecologic oncology. 2021;162:2021-03. doi:10.1016/s0090-8258(21)00775-7.(73) Joly F, Chabaud S, Cropet C, et al. Time without symptoms or toxicity (TWiST) in patients with newly diagnosed advanced ovarian cancer receiving maintenance olaparib or placebo plus bevacizumab: Analysis of PAOLA-1/ENGOT-ov25 phase III trial. Journal of Clinical Oncology. Conference: Annual Meeting				patients with high-grade ovarian cancer

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*
of the American Society of Clinical Oncology, ASCO. 2022;40(16 Supplement 1). doi:10.1200/jco.2022.40.16_suppl.5562.(74) Kurtz J, Anota A, Cropet C, et al. Quality of life in patients with advanced high-grade ovarian cancer (HGOC) receiving maintenance therapies after first-line (1L) chemotherapy in the randomized phase III PAOLA-1/ENGOT-ov25 trial (NCT02477644). Journal of Clinical Oncology. Conference: Annual Meeting of the American Society of Clinical Oncology, ASCO. 2022;40(16 Supplement 1). doi:10.1200/jco.2022.40.16_suppl.5560.(75) Labidi-Galy S, Rodrigues M, Sandoval J, et al. Efficacy of maintenance olaparib plus bevacizumab in patients with newly diagnosed advanced ovarian cancer according to BRCA mutation genotype in the phase III PAOLA-1/ENGOT-ov25 trial. Journal of Clinical Oncology. Conference: Annual Meeting of the American Society of Clinical Oncology, ASCO. 2022;40(16 Supplement 1). doi:10.1200/jco.2022.40.16_suppl.5571.(76) Labidi-Galy S, Rodrigues M, Sandoval J, et al. Association of location of BRCA1 and BRCA2 mutations with benefit from olaparib and bevacizumab maintenance in high-grade ovarian cancer: phase III PAOLA-1/ENGOT-ov25 trial subgroup exploratory analysis. Annals of Oncology. 2023;34(2):152-162. doi:10.1016/j.annonc.2022.11.003.(77) Lorusso D, Mouret-Reynier M, Harter P, et al. 32O 5-year (y) overall survival (OS) with maintenance olaparib (ola) plus bevacizumab (bev) by clinical risk in patients (pts) with newly diagnosed advanced ovarian cancer (AOC) in the phase III PAOLA-1/ENGOT-ov25 trial. ESMO open. 2023;8(1):2023-02. doi:10.1016/j.esmoop.2023.100812.(78) Montegut C, Falandry C, Cinieri S, et al. Safety and quality of life of first-line maintenance olaparib plus bevacizumab in older patients with advanced ovarian cancer in the paola-1 trial. International journal of gynecological cancer. 2021;Vol.31(SUPPL 1):A201-A202p. doi:10.1136/ijgc-2021-esgo.346.(79)				

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*
Ray-Coquard IL, Leary A, Pignata S, Cropet C, Martin AG, Bogner G, Yoshida H, Vergote IB, Colombo N, Maenpaa J, Selle F. LBA29 Final overall survival (OS) results from the phase III PAOLA-1/ENGOT-ov25 trial evaluating maintenance olaparib (ola) plus bevacizumab (bev) in patients (pts) with newly diagnosed advanced ovarian cancer (AOC). Annals of Oncology. 2022 Sep 1;33:S1396-7.(80) Pautier P, Harter P, Pisano C, et al. Progression-free survival (PFS) and second PFS (PFS2) by disease stage in patients (pts) with homologous recombination deficiency (HRD)-positive newly diagnosed advanced ovarian cancer receiving bevacizumab (bev) with olaparib/placebo maintenance in the phase III PAOLA-1/ENGOT-ov25 trial. Journal of Clinical Oncology. Conference: Annual Meeting of the American Society of Clinical Oncology, ASCO. 2021;39(15 SUPPL). doi:10.1200/jco.2021.39.15_suppl.5514.(81) Ray-Coquard I, Leary A, Pignata S, et al. Olaparib plus bevacizumab first-line maintenance in ovarian cancer: final overall survival results from the PAOLA-1/ENGOT-ov25 trial. Annals of Oncology. 2023;34(8):681-692. doi:10.1016/j.annonc.2023.05.005.(6) Sabatier R, Rousseau F, Joly F, et al. Efficacy and safety of maintenance olaparib and bevacizumab in ovarian cancer patients aged >=65 years from the PAOLA-1/ENGOT-ov25 trial. European Journal of Cancer. 2023;181:42-52. doi:10.1016/j.ejca.2022.11.029.(82) Sabatier R, Rousseau F, Joly F, et al. Efficacy and safety of maintenance olaparib and bevacizumab (bev) in ovarian cancer (OC) patients (pts) aged ≥65 years (y) from the PAOLA-1/ENGOT-ov25 first-line trial. Annals of oncolo Lorusso D, Mouret-Reynier M, Harter P, et al. Updated progression-free survival and final overall survival with maintenance olaparib plus bevacizumab according to clinical risk in patients with newly diagnosed advanced ovarian cancer in the phase III PAOLA-1/ENGOT-ov25 trial. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2024;34(4):550-558. doi:10.1136/ijgc-2023-004995.gy. 2021;32:S737-S738. doi:10.1016/j.annonc.2021.08.1181.(83)				

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*
Schouten P, Schmidt S, Becker K, et al. Olaparib Addition to Maintenance Bevacizumab Therapy in Ovarian Carcinoma With BRCA-Like Genomic Aberrations. JAMA network open. 2024;7(4):e245552. doi:10.1001/jamanetworkopen.2024.5552.(84)				

* 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

EQ-5D-5L and FACT-O were collected in the ATHENA-MONO trial; FACT-O data were extracted from the primary publication(7, 27) and clinical study report, whereas EQ-5D-5L was extracted from the clinical study report(27). In the PRIMA trial, EORTC QLQ-C30, FOSI, and EORTC QLQ-OV28 were collected. Data on EORTC QLQ-C30 were extracted from the primary publication(5) and CT.gov records(85), whereas results for FOSI and EORTC QLQ-OV28 were extract from CT.gov records(85). EORTC QLQ-C30 was included in the PAOLA-1 trial; results were extracted from the primary publication(10). An overview of the relevant literature in HRQoL is summarised in Table 12.

Table 12 Relevant literature included for (documentation of) health-related quality of life (See section 0)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Monk BJ, Parkinson C, Lim MC, et al. A Randomized, Phase III Trial to Evaluate Rucaparib Monotherapy as Maintenance Treatment in Patients With Newly Diagnosed Ovarian Cancer (ATHENA-MONO/GOG-3020/ENGOT-ov45). Journal of Clinical Oncology : official journal of the American Society of Clinical Oncology. Dec 1 2022;40(34):3952-3964. doi:10.1200/jco.22.01003(7)	EQ-5D-5L results	Section 10.1
	FACT-O TOI results	Section 10.2

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Clovis Oncology Inc (formar MAH of Rucaparib) ATHENA-MONO Interim Clinical Study Report (27)		
Monk B, Barretina-Ginesta M, Pothuri B, et al. Niraparib first-line maintenance therapy in patients with newly diagnosed advanced ovarian cancer: final overall survival results from the PRIMA/ENGOT-OV26/GOG-3012 trial. Annals of oncology : official journal of the European Society for Medical Oncology. 2024;doi:10.1016/j.annonc.2024.08.2241.(5) ClinicalTrials.gov; NCT02655016: A Study of Niraparib (GSK3985771) Maintenance Treatment in Participants With Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy (85)	EORT QLQ-C30 FOSI EORTC QLQ-OV28	Section 10.3 Section 10.4 Section 10.5
Ray-Coquard I, Pautier P, Pignata S, et al. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. The New England journal of medicine. Dec 19 2019;381(25):2416-2428. doi:10.1056/NEJMoa1911361(10)	EORT QLQ-C30	Section 10.3

5.3 Literature used for inputs for the health economic model

A cost comparison was conducted for drug acquisition costs and monitoring costs. The costs of niraparib, olaparib, and bevacizumab were sourced from medicinpriser.dk(86) (Table 13).

Table 13 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
Publicly available sources/literature	Medicine costs	According to DMC guidelines, medicine costs were sourced from medicinpriser.dk (86)	
Publicly available sources/literature	Monitoring and disease management costs	According to DMC guidelines, healthcare resource use costs were sourced from DRG TAKSTER (87)	

6. Efficacy

6.1 Efficacy of rucaparib compared to niraparib for the non-tBRCA, HRD+ cohort

6.1.1 Relevant studies

This section describes the comparison of rucaparib with niraparib, which is the comparator for patients with ovarian cancer in the non-tBRCA, HRD+ subgroup in this submission. Given the lack of direct head-to-head trial data comparing rucaparib and niraparib, a comparative analysis was conducted using the ATHENA-MONO (NCT03522246) and PRIMA (NCT02655016) studies.(7, 54)

ATHENA-MONO is a randomised, double-blind, placebo-controlled, phase 3 trial evaluating the efficacy and safety of rucaparib for the maintenance treatment of ovarian cancer after 1L platinum-based chemotherapy.(7) ATHENA-MONO, which provided the pivotal basis for the regulatory approval of rucaparib in this indication, was conducted in 200 centres in 24 countries, including Denmark.(27, 88) ATHENA-MONO is currently ongoing, with final analysis to be conducted upon death of 70% of study participants.(7) An overview of the ATHENA-MONO study is presented in Table 14. More information can be found in Appendix A.

PRIMA is a randomised, double-blind, placebo-controlled, phase 3 trial evaluating the efficacy and safety of niraparib for the maintenance treatment of ovarian cancer after 1L platinum-based chemotherapy.(54) PRIMA, which provided the pivotal basis for the regulatory approval of rucaparib in this indication, was conducted in 181 centres in 20 countries, including Denmark.(54) The final OS results were published with an 8 April 2024 data cut-off (DCO; median follow-up 73.9 months).(5) An overview of the PRIMA study is presented in Table 14. More information can be found in Appendix A.

Table 14 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
ATHENA-MONO, NCT03522246 Monk et al. 2022(7)	Randomised, double blinded, placebo-controlled, phase 3 study of rucaparib vs. placebo.	Primary DCO: 23 March 2022 (median follow-up 26 months) Latest DCO: 17 May 2024 (median follow-up 4 years)(39) The study is ongoing.	Adult patients with ovarian cancer who had achieved an investigator-assessed response to 1L platinum-based chemotherapy.	Oral rucaparib 600 mg twice per day starting on cycle 1 day 1 in 28-day cycles plus intravenous placebo once every four weeks for up to 24 months or until disease progression, death or unacceptable toxicity.	Matching placebo administered orally twice per day starting on cycle 1 day 1 in 28-day cycles plus intravenous placebo once every four weeks for up to 24 months.	Primary endpoint was invPFS. Secondary endpoints were BICR-assessed PFS, OS, ORR and DOR. Exploratory endpoints were PFS2, FACT-O, EQ-5D-5L, CFI, TFST, TSST and TTD. Safety was assessed through the monitoring of adverse events, laboratory testing, measurement of vital signs, and physical examination. The pre-specified DCO for ATHENA-MONO was 23 March 2022, with a median follow-up of 26 months.(7) An additional year of follow-up was presented to the EMA for OS, CFI, TFST, TSST and TTD with a DCO of 9 March 2023(42). An additional ad-hoc analysis for invPFS and PFS2 is dated 17 May 2024 (approximately 4 years follow-up)(39). The most recent analysis for invPFS, PFS2, TFST is dated 5 May 2025 (5 years follow-up)(53).
PRIMA, NCT02655016 González-Martín et al. 2019(54)	Randomised, double blinded, placebo-controlled, phase 3 study of niraparib vs. placebo.	Primary DCO: 17 May 2019 (median follow-up 13.8 months) Final DCO: 8 April 2024 (median follow-up 73.9 months)(5)	Adult patients with ovarian cancer who had achieved an investigator-assessed response to 1L platinum-based chemotherapy.	Oral niraparib 300 mg (or 200 mg if weight <77 kg and/or platelet count <150,000 cm3) once daily in 28-day cycles for up to 36 months	Matching placebo administered orally once daily in 28-day cycles for up to 36 months.	Primary endpoint was BICR PFS. Secondary endpoints were OS, TFST, PFS2, pharmacokinetic analyses, FOSI, EQ-5D-5L, EORTC-QLQ-C30/OV28. Safety was assessed through the monitoring of adverse events, laboratory testing, measurement of vital signs, and physical examination. The pre-specified DCO for PRIMA was 17 May 2019, with a median follow-up of 13.8 months.(54) The final OS analysis had a DCO of 8 April 2024 (median follow-up 73.9 months).(5)

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
				until disease progression.		

Abbreviations: 1L = first-line; BICR = blinded independent central review; CFI = chemotherapy-free interval; DCO = data cut-off; DOR = duration of response; EORTC-QLQ-C30/OV28 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30/Ovarian Cancer Module; EQ-5D-5L = EuroQol 5 Dimension 5 Level; FACT-O = Functional Assessment of Cancer Therapy – Ovarian; HRD = homologous recombination deficiency; invPFS = investigator-assessed progression-free survival; PFS = progression-free survival; ORR = overall response rate; OS = overall survival; TFST = time to first subsequent therapy; TSST = time to second subsequent therapy; tBRCA = tumour tissue mutation in breast cancer gene; TTD = time to treatment discontinuation

6.1.2 Comparability of studies

Eligibility criteria between ATHENA-MONO and PRIMA are summarised in Table 15. A key difference between studies is that the intention-to-treat (ITT) population for PRIMA was patients with newly diagnosed aOC that met a pre-specified high risk definition(89). ATHENA-MONO included patients with stage III-IV high-grade ovarian cancer undergoing surgical cytoreduction (R0/complete resection permitted) and responding to first-line platinum-doublet chemotherapy but did not restrict the population to high risk patients.(7) The patient population for ATHENA-MONO included patients without certain prognostically high-risk clinical characteristics and could be considered more real-world compared to other studies.(7)

Table 15 Comparison of key eligibility criteria for ATHENA-MONO(7) and PRIMA(54)

	ATHENA-MONO(7)	PRIMA(54)
Age	≥18 years	≥18 years
Population	Newly diagnosed, histologically confirmed, advanced (FIGO stage III-IV), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer. The inclusion criteria did not restrict patients by HRD status or surgical outcome. Patients with neoadjuvant therapy and visible residual disease were also included.	Newly diagnosed, histologically confirmed advanced (FIGO stage III-IV) cancer of the ovary, peritoneum, or fallopian tube. Included in this category were patients with stage III disease with visible residual tumour after primary debulking surgery, inoperable stage III disease, or any stage IV disease, as well as those who had received neoadjuvant chemotherapy.
Prior chemotherapy	4 to 8 cycles of 1L platinum-doublet treatment, including a minimum of four cycles of a platinum/taxane combination (bevacizumab was only allowed during the chemotherapy phase).	6 to 9 cycles of first-line platinum-based chemotherapy, with ≥2 post-operative cycles of platinum-based therapy following interval debulking surgery. Patients who received bevacizumab with their chemotherapy could be included as long as the last dose of bevacizumab was received ≥ 28 days prior to signing the main informed consent form.
Treatment response	Response, in the opinion of the investigator, defined as no evidence of disease progression radiologically or through rising CA-125 at any time during front-line treatment; and: No evidence of measurable disease by RECIST v1.1 (if complete resection/R0 at	Complete or partial response according to investigator assessment after ≥3 cycles of therapy. Patients must have either CA-125 in the normal range or CA-125 decrease during their 1L therapy that is

	primary or interval cytoreductive surgery); or A partial or complete response per RECIST v1.1 (if measurable disease was present after surgery and prior to chemotherapy); or A GCIG CA-125 response (if only non-measurable disease was present after surgery and prior to chemotherapy)(90)	stable for at least 7 days (i.e., no increase >15% from nadir).
Mutation testing	FoundationOne	Myriad myChoice® test
ECOG PS	0-1	Not applicable

Abbreviations: 1L = first-line; BRCA = breast cancer gene; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HRD = homologous recombination deficiency; FIGO = International Federation of Gynecology and Obstetrics

6.1.2.1 Comparability of patients across studies

The ATHENA-MONO HRD+ population included 185 patients in the rucaparib arm and 49 patients in the placebo arm. The rucaparib and placebo arms in the ATHENA-MONO were matched for all available EMs against the niraparib and placebo arms in PRIMA HRD+ population, respectively. The matching factors included risk category, ECOG performance score, FIGO stage, neoadjuvant chemotherapy, response after chemotherapy, CA-125 level, and BRCA mutation status.

The matching resulted in an ESS of [redacted] for rucaparib, which corresponds to [redacted] of the rucaparib HRD+ population, and an ESS of [redacted] for placebo, which corresponds to [redacted] of the placebo HRD+ population. Table 16 presents the baseline characteristics of the rucaparib and placebo arms in the ATHENA-MONO HRD+ population before and after matching, in comparison to niraparib and placebo arms in PRIMA HRD+ population. Distribution of weights are provided in Appendix C.2.

Table 16 Baseline characteristics of patients in ATHENA-MONO and PRIMA included for the comparative analysis of efficacy and safety in HRD+ population (27, 91)

Variable (%)	Rucaparib arm, ATHENA-MONO (n=185)	Weighted rucaparib arm, ATHENA-MONO (ESS=[redacted])	Niraparib arm, PRIMA (n=247)	Placebo arm, ATHENA-MONO (n=49)	Weighted placebo arm, ATHENA-MONO (ESS=[redacted])	Placebo arm, PRIMA (n=126)
Risk category: high	71.9%	[redacted]	100.0%	73.5%	[redacted]	100.0%
Age: ≤58 years (median for PRIMA)	51.9%	[redacted]	50.0%	46.9%	[redacted]	50.0%
ECOG PS: 0	71.4%	[redacted]	73.7%	79.6%	[redacted]	77.0%
ECOG PS: 1	28.6%	[redacted]	26.3%	20.4%	[redacted]	23.0%
FIGO stage: III	73.5%	[redacted]	65.2%	63.3%	[redacted]	61.9%
FIGO stage: IV	26.5%	[redacted]	34.8%	36.7%	[redacted]	38.1%
Neoadjuvant chemotherapy: yes	43.8%	[redacted]	63.2%	44.9%	[redacted]	63.5%
Neoadjuvant chemotherapy: no	56.2%	[redacted]	36.8%	55.1%	[redacted]	36.5%
Response after chemotherapy: NED or CR	68.1%	[redacted]	74.9%	69.4%	[redacted]	73.8%
Response after chemotherapy: PR	17.8%	[redacted]	25.1%	18.4%	[redacted]	26.2%
Response after chemotherapy: Unevaluable	14.1%	[redacted]	0.0%	12.2%	[redacted]	0.0%

Variable (%)	Rucaparib arm, ATHENA-MONO (n=185)	Weighted rucaparib arm, ATHENA-MONO (ESS=[redacted])	Niraparib arm, PRIMA (n=247)	Placebo arm, ATHENA-MONO (n=49)	Weighted placebo arm, ATHENA-MONO (ESS=[redacted])	Placebo arm, PRIMA (n=126)
N. of cycle of platinum-based chemotherapy: 6	63.8%	[redacted]	76.0%	63.3%	[redacted]	75.0%
N. of cycle of platinum-based chemotherapy: ≥7	36.2%	[redacted]	24.0%	36.7%	[redacted]	25.0%
CA-125: ≤ ULN	87.0%	[redacted]	96.3%	93.9%	[redacted]	96.0%
CA-125: ≥ ULN	13.0%	[redacted]	3.7%	6.1%	[redacted]	4.0%
BRCA mutation status: Yes	49.2%	[redacted]	61.5%	49.0%	[redacted]	56.3%
BRCA mutation status: No	50.8%	[redacted]	38.5%	51.0%	[redacted]	43.7%

Abbreviations: BRCA, tumor tissue mutation in breast cancer gene; Non-tBRCA, BRCA wild-type (non-mutated state); CA-125, cancer antigen 125; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, estimated sample size; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; HRD, homologous recombination deficiency; NED, no evidence of disease; PR, partial response; ULN, upper limit of normal

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

No input related to patient characteristics was included in the cost comparison analysis. Therefore, Table 17 is not applicable.

Table 17 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model (reference if relevant)
N/A	N/A	N/A

6.1.4 Efficacy – results per ATHENA-MONO in the non-tBRCA HRD+ population

Trial data presented in this submission for ATHENA-MONO are based on:

- The pre-specified DCO of 23rd March 2022 (invPFS, OS, overall response rate (ORR), and safety analysis)(7),
- Ad-hoc analyses of 9 March 2023 (OS, chemotherapy-free interval [CFI], time to first subsequent therapy [TFST], time to second subsequent therapy [TSST], and time to treatment discontinuation [TDT])(42, 92),
- 17 May 2024 (invPFS and PFS2)(39, 43, 44),
- 5 May 2025 for invPFS, PFS2, and TFS(53).

The latest results for OS, investigator-assessed PFS, and PFS2 are included in this section.

6.1.4.1 invPFS

At the DCO of 17 May 2024, rucaparib significantly reduced the risk of disease progression among patients in the non-tBRCA, HRD+ cohort who had responded to 1L platinum-doublet treatment, as assessed by the investigators.(39, 43)

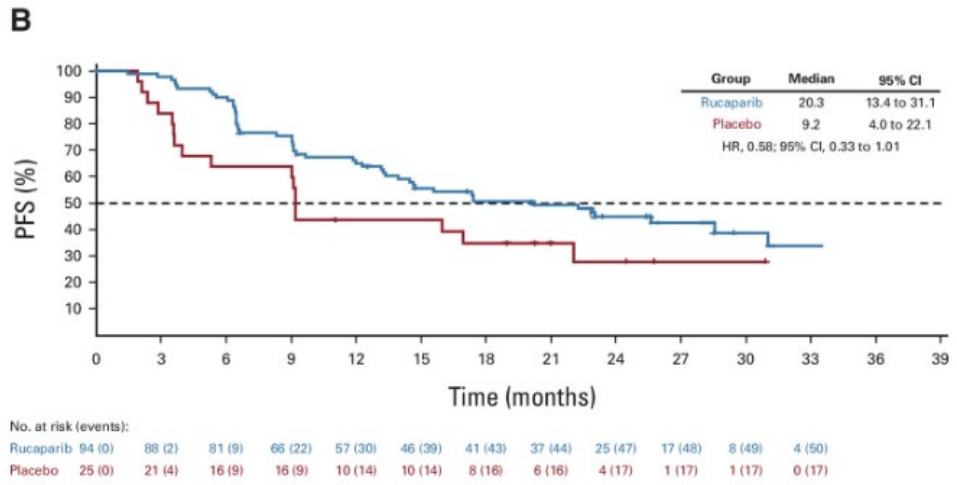
Table 18 Summary of invPFS in the ITT population and non-tBRCA, HRD+ cohort

	ITT		non-tBRCA, HRD+	
	Rucaparib (n=427)	Placebo (n=111)	Rucaparib (n=94)	Placebo (n=25)
23 March 2022 DCO(7, 27)				
Median invPFS, months (95% CI)	20.2 (15.2, 24.7)	9.2 (8.3, 12.2)	20.3 (13.4, 31.1)	9.2 (4.0, 22.1)
HR (95% CI); p value	0.52 (0.40, 0.68); <0.001		0.58 (0.33, 1.01); 0.0524	

17 May 2024 DCO(39, 43)				
Median invPFS, months (95% CI)	20.2 (15.6, 23.9)	9.2 (8.5, 12.2)	22.3 ([redacted])	9.2 ([redacted])
HR (95% CI); log-rank test	0.58 (0.45,0.74); <0.001		0.58 (0.35, 0.96); [redacted]	
5 May 2025 DCO(53)				
Median invPFS, months (95% CI)	20.2 (15.6, 24.0)	9.2 (8.5, 12.2)	22.3	9.2
HR (95% CI); log-rank test	0.53 (0.42,0.69); <0.001		0.58 (0.35, 0.96)	

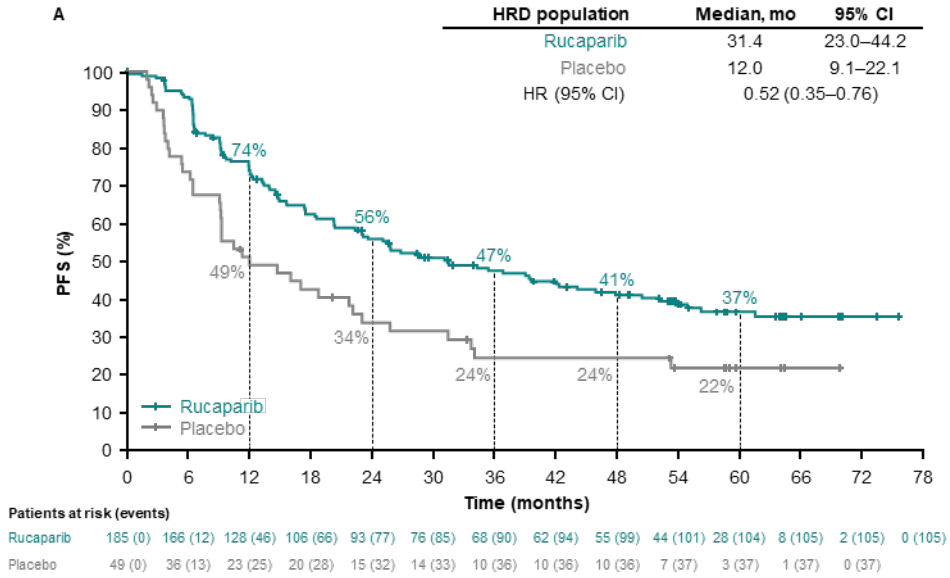
Abbreviations: CI = confidence interval; DCO = data cut-off; HR = hazard ratio; HRD = homologous recombination deficiency; invPFS = investigator-assessed progression-free survival; ITT = intention to treat; tBRCA = tumour tissue mutation in breast cancer gene

Figure 2 invPFS KM curve (non-tBRCA, HRD+ population) - ATHENA-MONO(7)



NOTE: DCO 23 March 2022 for non-tBRCA, HRD+ population

Figure 3 invPFS KM curve (HRD+ population)- ATHENA-MONO(53)



NOTE: DCO 5 May 2025 for HRD+ population

6.1.4.2 OS

As of 23 March 2022, the OS results were very immature (<70% death events) with only 24.7% of events occurring in the ITT population.(7, 27, 42) Interim OS was determined using the Cox proportional hazard model.(27) At the ad-hoc analysis (9 March 2023), the proportion of death events had increased to 35% for the ITT population but OS results were still immature.(42) OS results trended in favour of rucaparib over placebo in the non-tBRCA, HRD+ cohort, but statistical significance was not reached.(42) The final OS analysis will be performed once 70% of death events have been collected.(27)

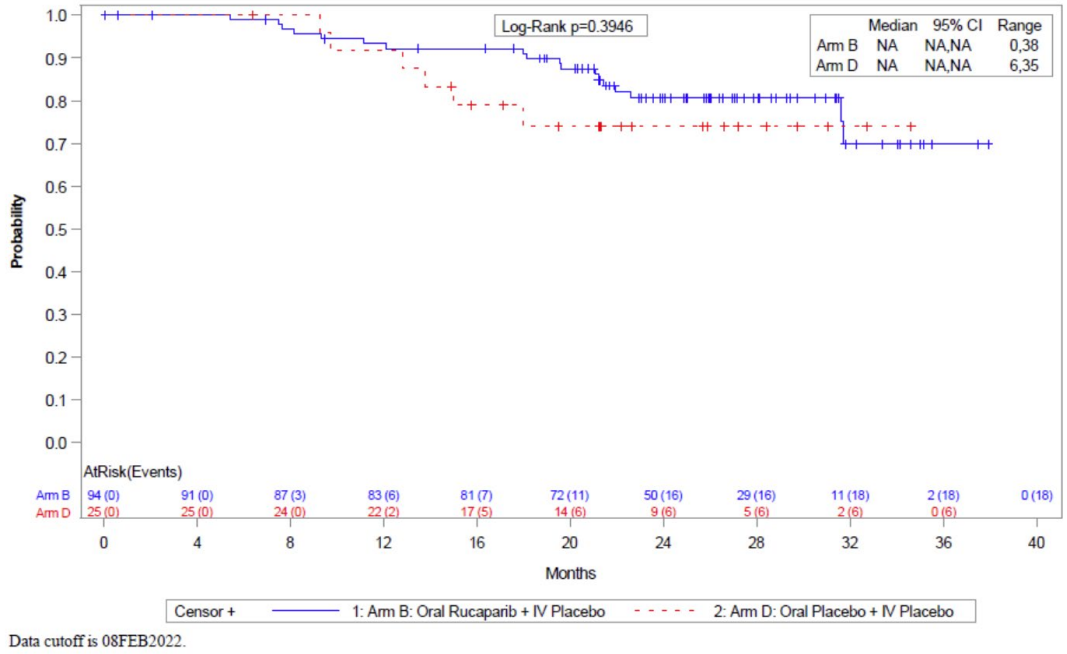
Table 19 Summary of OS in the ITT population and non-tBRCA, HRD+ cohort

	ITT		non-tBRCA, HRD+	
	Rucaparib (n=427)	Placebo (n=111)	Rucaparib (n=94)	Placebo (n=25)
23 March 2022 DCO(27)				
Median OS, months (95% CI)	38.8 (38.8, NR)	NR (31.4, NR)	NR (NR, NR)	NR (NR, NR)
HR (95% CI); p value	0.96 (0.63, 1.47); 0.8688		0.64 (0.25, 1.59); 0.3331	
9 March 2023 DCO(53)				
Median OS, months (95% CI)	NR	46.2 (34.6, NR)	NR	[redacted]

HR (95% CI); log-rank test	0.83 (0.58, 1.17)	[redacted]

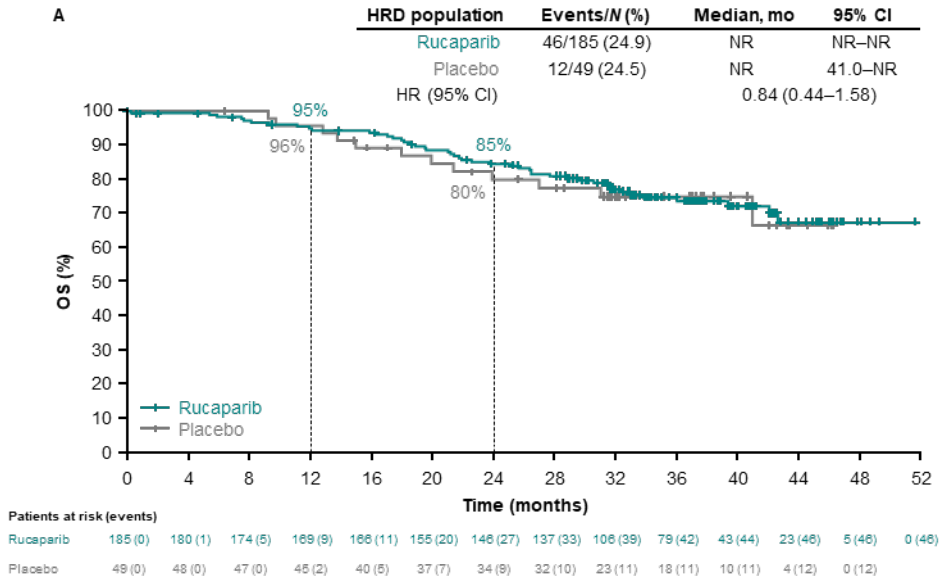
Abbreviations: CI = confidence interval; DCO = data cut-off; HR = hazard ratio; HRD = homologous recombination deficiency; ITT = intention to treat; NR = not reached; OS = overall survival; tBRCA = tumour tissue mutation in breast cancer gene

Figure 4 OS KM curve - ATHENA-MONO(42)



Note: DCO 8 Feb 2022; KM curve is for non-tBRCA HRD+ population

Figure 5 OS KM curve (HRD+) - ATHENA-MONO(53)



Note: DCO 5 May 2025; KM curve is for HRD+ population

6.1.4.3 PFS2

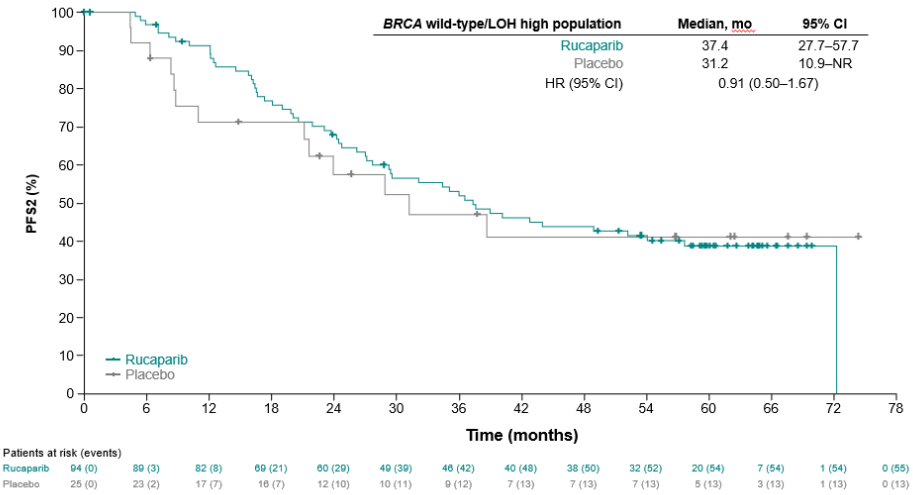
About [redacted] in the ITT population initiated at least one regimen of subsequent anticancer therapy at the 23 March 2022 DCO. Of these, [redacted] patients in the rucaparib group and [redacted] patients in the placebo group received subsequent PARPi therapy.(27, 42) At the latest DCO (17 May 2024), rucaparib significantly improved PFS2 over placebo in the ITT population and PFS2 trended in favour or rucaparib in the non-tBRCA, HRD+ cohort.(42, 43)

Table 20 Summary of PFS2 in the ITT population and non-tBRCA, HRD+ cohort

	ITT		non-tBRCA, HRD+	
	Rucaparib (n=427)	**Placebo (n=111)**	**Rucaparib (n=94)**	**Placebo (n=25)**
23 March 2022 DCO(42)				
HR (95% CI); p value	0.88 (0.63, 1.22); 0.440		Not reported	
17 May 2024 DCO(43, 44)				
Median PFS2, months	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI); Log-rank test	[redacted]		[redacted]	
5 May 2025 DCO(53)				
Median PFS2, months	35.1 (29.4, 41.2)	26.9 (21.7, 31.5)	37.4	31.2
HR (95% CI); Log-rank test	0.72 (0.55, 0.93)		0.91 (0.50, 1.67)	

Abbreviations: CI = confidence interval; DCO = data cut-off; HR = hazard ratio; HRD = homologous recombination deficiency; ITT = intention to treat; NR = not reached; PFS2 = progression-free survival to second progression; tBRCA = tumour tissue mutation in breast cancer gene

Figure 6 PFS2 KM curve - ATHENA-MONO – non-tBRCA HRD+ population (53)



6.1.5 Efficacy – results per ATHENA-MONO in HRD+ population (used in the MAIC)

Following feasibility assessment, the MAIC was conducted in the HRD+ population. Data for PFS, PFS2, and OS used in the MAIC is summarized in Table 21.

Table 21 Summary of effficacy – ATHENA-MONO, HRD+ population (used in the MAIC)

	HRD+	
	Rucaparib (n=185)	**Placebo (n=49)**
invPFS (DCO 17MAY 2024)(28)		
Median invPFS, months	[redacted]	[redacted]
HR (95% CI); Log-rank test	[redacted]	
PFS2 (DCO 17 MAY 2024)(28)		
Median PFS2, months	57.3	39.9
HR (95% CI); Log-rank test	0.74 (0.47, 1.17); [redacted]	
OS (DCO 9 MAR 2023)(53)		
Median OS, months	NR (NR-NR)	NR (41.0-NR)
HR (95% CI); Log-rank test	0.84 (0.44, 1.58); p=0.5811	

Abbreviations: CI = confidence interval; DCO = data cut-off; HR = hazard ratio; HRD = homologous recombination deficiency; NR = not reached; PFS2 = progression-free survival to second progression; OS = overall survival

6.1.6 Efficacy – results per PRIMA

The efficacy outcomes in the non-tBRCA, HRD+ population of the PRIMA study were sourced from Monk et al. 2024 with a DCO of 8 April 2024.(5) While treatment with niraparib significantly prolonged BICR-assessed PFS over placebo, there was no significant increase in OS or PFS2 with niraparib.(5) The most up-to-date published KM curves in the population most relevent to this assessment are presented in Figure 7 and Figure 8. KM curves for PFS2 were not reported. Following feasibility assessment, the MAIC was conducted in the HRD+ population. Data for PFS, PFS2, and OS used in the MAIC is summarized in Table 23.

Table 22 Summary of 8 April 2024 DCO outcomes from the PRIMA study(5)

	ITT		non-tBRCA, HRD+	
	Niraparib (n=487)	Placebo (n=246)	Niraparib (n=94)	Placebo (n=25)
Median invPFS, months	13.8	8.2	19.4	10.4
HR (95% CI)	0.66 (0.55, 0.78)		0.67 (0.45, 1.00)	
Median OS, months	46.6	48.8	Not reported	Not reported
HR (95% CI); p value	1.01 (0.84, 1.23); 0.8834		0.97 (0.62, 1.53)	
Median PFS2	30.1	27.6	38.0	34.1
HR (95% CI); p value	0.96 (0.79, 1.17)		0.88 (0.57, 1.36)	

Abbreviations: CI = confidence interval; DCO = data cut-off; HR = hazard ratio; HRD = homologous recombination deficiency; invPFS = investigator-assessed progression-free survival; ITT = intention to treat; PFS2 = progression-free survival to second progression; OS = overall survival; tBRCA = tumour tissue mutation in breast cancer gene

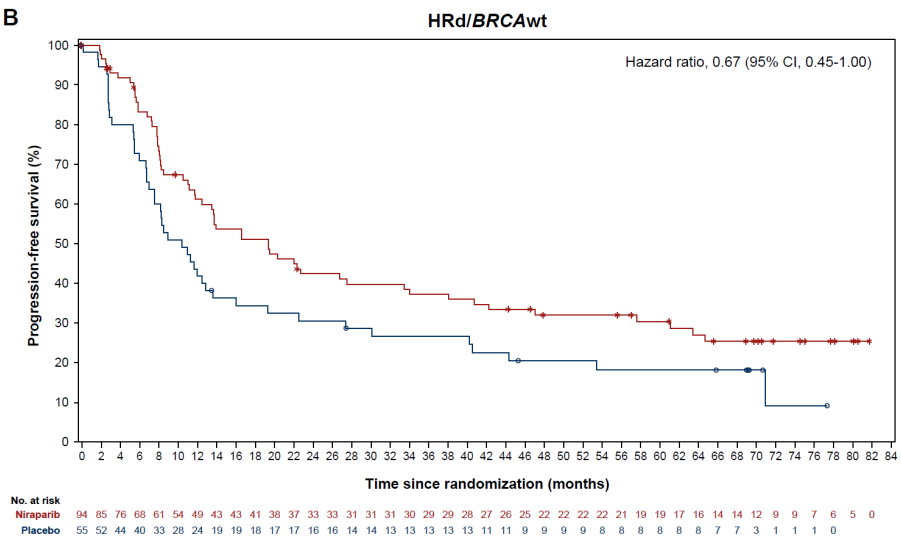
Table 23 Summary of effficacy –PRIMA, HRD+ population (used in the MAIC)

	HRD+	
	Niraparib (n=185)	Placebo (n=49)
invPFS (DCO 8 APR 2024) (5)		
Median invPFS, months	24.5	11.2
HR (95% CI); Log-rank test	0.51 (0.40, 0.66)	
PFS2 (DCO 8 APR MAY 2024) (5)		
Median PFS2, months	43.4	39.3

HR (95% CI); Log-rank test	0.87 (0.66, 1.17)	
OS (DCO 8 APR 2024) (5)		
Median OS, months	71.9	69.8
HR (95% CI); Log-rank test	0.95 (0.70, 1.29)	

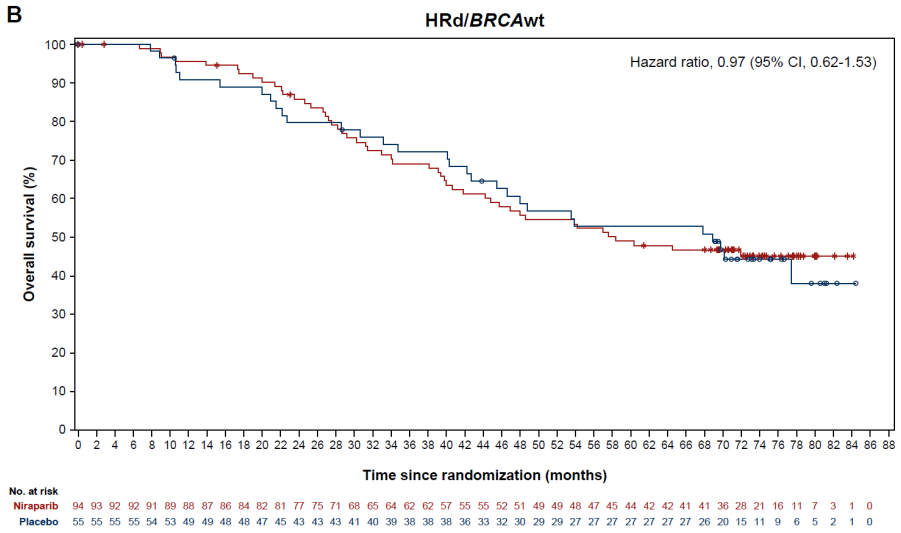
Abbreviations: CI = confidence interval; DCO = data cut-off; HR = hazard ratio; HRD = homologous recombination deficiency; NR = not reached; PFS2 = progression-free survival to second progression; OS = overall survival

Figure 7 PFS KM curve – PRIMA(5)



Note: KM plot is for non-tBRCA HRD+ patients

Figure 8 OS KM curve – PRIMA(5)



Note: KM plot is for non-tBRCA HRD+ patients

6.2 Efficacy of rucaparib compared to olaparib in combination with bevacizumab

6.2.1 Relevant studies

This section describes the comparison of rucaparib with olalarib in combination with bevacizumab. Given the lack of direct head-to-head trial data comparing rucaparib and bevacizumab, a comparative analysis was conducted using the ATHENA-MONO (NCT03522246) and PAOLA-1 (NCT02477644) studies.(7, 10) ATHENA-MONO efficacy results have been described in detail in Section 6.1.4. An overview of the ATHENA-MONO study is presented in Table 14. More information can be found in Appendix A.

PAOLA-1 is a randomised double-blind, phase 3 trial evaluating the efficacy and safety of olaparib plus bevacizumab vs. placebo plus bevacizumab for the maintenance treatment of ovarian cancer after 1L platinum-based chemotherapy plus bevacizumab.(10) PAOLA-1 was conducted in 11 countries, including Denmark.(10) The final OS results were published with a 22 March 2022 DCO (median follow-up 61.7 months with olaparib plus bevacizumab; 61.9 months with placebo plus bevacizumab).(6) An overview of the PAOLA-1 study is presented in Table 24. More information can be found in Appendix A.

Table 24 Overview of study design for studies included in the comparison for rucaparib versus olaparib with bevacizumab

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
PAOLA-1, NCT02477644 Ray-Coquard et al. 2019(6, 10)	Randomised, double blinded, phase III study of olaparib plus bevacizumab vs. placebo plus bevacizumab.	Primary DCO: 22 March 2019 (median follow-up of 22.9 months) Final DCO: 22 March 2022 (median follow-up 61.7 months with olaparib plus bevacizumab; 61.9 months with placebo plus bevacizumab)(6)	Adult patients with FIGO III or IV, high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian tube cancer or nonmucinous epithelial ovarian cancers with germline BRCA mutation who responded to 1L treatment with platinum-based chemotherapy plus bevacizumab.	Oral olaparib 300 mg twice daily at least 3 and no more than 9 weeks after the last dose of chemotherapy for up to 24 months. Intravenous bevacizumab, initiated with chemotherapy and continued as maintenance therapy, at a dose of 15 mg/kg of body weight every 3 weeks for a total duration of 15 months.	Matching placebo administered orally twice daily at least 3 and no more than 9 weeks after the last dose of chemotherapy for up to 24 months. Intravenous bevacizumab, initiated with chemotherapy and continued as maintenance therapy, at a dose of 15 mg/kg of body weight every 3 weeks for a total duration of 15 months.	Primary endpoint was invPFS (plus subgroup analyses of BICR PFS). Secondary endpoints were PFS2, OS, TSFT, EORTC-QLQ-C30 Safety was assessed through the monitoring of adverse events. The pre-specified DCO for PAOLA-1 was 22 March 2019, with a median follow-up of 22.9 months.(10) The final OS analysis had a DCO 22 March 2022 (median follow-up 61.7 months with olaparib plus bevacizumab; 61.9 months with placebo plus bevacizumab months).(6)

Abbreviations: 1L = first-line; BICR = blinded independent central review; DCO = data cut-off; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HRD= homologous recombination deficiency; invPFS = investigator-assessed progression-free survival; OS = overall survival; tBRCA = tumour tissue mutation in breast cancer gene; TSFT = time to first subsequent therapy

6.2.2 Comparability of studies

Eligibility criteria between ATHENA-MONO and PAOLA-1 are summarised in Table 25. A key difference between studies is that PAOLA-1 only included patients who received bevacizumab alongside chemotherapy as a 1L treatment prior to maintenance therapy,(10) while ATHENA-MONO included a mix of patients with and without bevacizumab induction therapy.(7)

Table 25 Comparison of eligibility criteria for ATHENA-MONO and PAOLA-1

	ATHENA-MONO(7)	PAOLA-1(10)
Age	≥18 years	≥18 years
Population	Newly diagnosed, histologically confirmed, advanced (FIGO stage III-IV), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer. The inclusion criteria did not restrict patients by HRD status or surgical outcome. Patients with neoadjuvant therapy and visible residual disease were also included.	Newly diagnosed advanced (FIGO stage III or IV), high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian tube cancer. Patients with other non-mucinous epithelial ovarian cancers were eligible, provided they had a deleterious germline BRCA1 or BRCA2 mutation.
Prior chemotherapy	4 to 8 cycles of 1L platinum-doublet treatment, including a minimum of four cycles of a platinum/taxane combination (bevacizumab was only allowed during the chemotherapy phase).	1L treatment with platinum–taxane chemotherapy (typically carboplatin and paclitaxel) plus bevacizumab. After completing 6 cycles of chemotherapy, patients who achieved a clinical complete or partial response were eligible for maintenance therapy. Maintenance treatment with olaparib or placebo began 3 to 9 weeks after the last dose of chemotherapy and continued for up to 24 months. Bevacizumab was administered at a dose of 15 mg/kg every 3 weeks for a total duration of 15 months, including the time it was given with chemotherapy.
Treatment response	Response, in the opinion of the investigator, defined as no evidence of disease progression radiologically or through rising CA-125 at any time during front-line treatment; and: No evidence of measurable disease by RECIST v1.1 (if complete resection/R0 at primary or interval cytoreductive surgery); or	No evidence of disease, CR or PR.

	ATHENA-MONO(7)	PAOLA-1(10)
	A partial or complete response per RECIST v1.1 (if measurable disease was present after surgery and prior to chemotherapy); or A GCIG CA-125 response (if only non-measurable disease was present after surgery and prior to chemotherapy)	
Mutation testing	FoundationOne	Myriad myChoice® test
ECOG PS	0-1	0-1

Abbreviations: 1L = first-line; BRCA = breast cancer gene; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HRD = homologous recombination deficiency; FIGO = International Federation of Gynecology and Obstetrics; PR = partial response

6.2.2.1 Comparability of patients across studies

The ATHENA-MONO HRD+ population included 185 patients in the rucaparib arm. The rucaparib arm in ATHENA-MONO was matched for all available EMs and PFs against the olaparib + bevacizumab arm in PAOLA-1 HRD+ population. The matching factors included ECOG performance score, tumor location, FIGO stage, histology, history of surgery, response after chemotherapy, CA-125 level, and BRCA mutation status (7, 10, 27).

The matching resulted in an ESS of [redacted], which corresponds to [redacted] of the rucaparib HRD+ population. Table 26 presents the baseline characteristics of the rucaparib arm in the ATHENA-MONO study both before and after matching, in comparison to the olaparib + bevacizumab arm in the PAOLA-1 HRD+ population (7, 10, 27). Distribution of weights are provided in Appendix C.2.

Table 26 Baseline characteristics of patients in ATHENA-MONO and PAOLA-1 included for the comparative analysis of efficacy and safety in the HRD+ population (7, 10, 27, 91)

Variable (%)	Rucaparib arm, ATHENA-MONO (N=185)	Weighted rucaparib arm, ATHENA-MONO (ESS=[redacted])	Olaparib+ bevacizumab arm, PAOLA-1 (N=255)
Age ≤58 years (median for PAOLA-1)	51.9%	[redacted]	50.0%
ECOG PS: 0	71.4%	[redacted]	75.7%
ECOG PS: 1	28.6%	[redacted]	24.3%
Tumour location: ovary	82.7%	[redacted]	85.1%
Tumour location: fallopian tube	11.4%	[redacted]	9.4%

Variable (%)	Rucaparib arm, ATHENA-MONO (N=185)	Weighted rucaparib arm, ATHENA-MONO (ESS=[redacted])	Olaparib+ bevacizumab arm, PAOLA-1 (N=255)
Tumour location: peritoneal	5.9%	[redacted]	5.5%
FIGO stage: III	73.5%	[redacted]	71.4%
FIGO stage: IV	26.5%	[redacted]	28.6%
Histology: serous	94.1%	[redacted]	94.9%
Histology: endometrioid	3.2%	[redacted]	3.5%
Histology: mixed/other	2.7%	[redacted]	1.6%
History of surgery: upfront	56.2%	[redacted]	56.9%
History of surgery: interval	43.8%	[redacted]	39.2%
History of surgery: no surgery	0.0%	[redacted]	3.9%
Response after chemotherapy: NED or CR	68.1%	[redacted]	80.8%
Response after chemotherapy: PR	17.8%	[redacted]	19.2%
Response after chemotherapy: unevaluable	14.1%	[redacted]	0.0%
CA-125 ≤ULN	87.0%	[redacted]	89.4%
CA-125 >ULN	13.0%	[redacted]	10.6%
BRCA mutation: Yes	49.2%	[redacted]	62.0%
BRCA mutation: No	50.8%	[redacted]	38.0%

Abbreviations: CA-125 = cancer antigen 125; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group performance status; ESS = effective sample size; FIGO = Fédération Internationale de Gynécologie et d'Obstétrique; HRD = homologous recombination deficiency; NED = no evidence of disease; PR = partial response; tBRCA = tumour tissue mutation in breast cancer gene; ULN = upper limit of normal

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

No input related to patient characteristics was included in the cost comparison analysis. Therefore, Table 27 is not applicable.

Table 27 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model (reference if relevant)
N/A	N/A	N/A

6.2.4 Efficacy – results per ATHENA-MONO

Results for the ATHENA-MONO study are already presented presented in Section 6.1.4.

6.2.5 Efficacy – results per PAOLA-1 in the HRD+ population

The efficacy outcomes in HRD+ population of the PAOLA-1 study were sourced from Ray-Coquard et al. 2019 (22 March 2019 DCO)(10), González-Martín et al. 2022 (22 March 2020 DCO)(70) and Ray-Coquard et al. 2023 (22 March 2022 DCO).(6) The most up-to-date published KM curves in the population most relevent to this assessment are presented in Figure 9, Figure 10, and Figure 11.

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Table 28 Summary of outcomes from the PAOLA-1 study

	ITT		Non-tBRCA HRD+	
	Olaparib + bevacizumab (n=537)	Placebo + bevacizumab (n=269)	Olaparib + bevacizumab (n=97)	Placebo + bevacizumab (n=55)
invPFS - 22 March 2022 DCO(6)				
Median PFS, months	22.9 (21.9, 27.0)	16.6 (15.4, 18.6)	30.0 (21.9, 60.3)	16.6 (12.9, 19.5)
HR (95% CI); p value	0.63 (0.53, 0.74)		0.47 (0.32, 0.70)	
OS - 22 March 2022 DCO(6)				
Median OS, months	56.5	51.6	NR	52.0
HR (95% CI); p value	0.92 (0.76, 1.12); 0.4118		0.71 (0.45, 1.13)	
PFS2 - 22 March 2020 DCO(70)				
Median PFS2	36.5	32.6	50.3	30.1

HR (95% CI); p value	0.78 (0.64, 0.95); 0.0125	0.60 (0.38, 0.96)

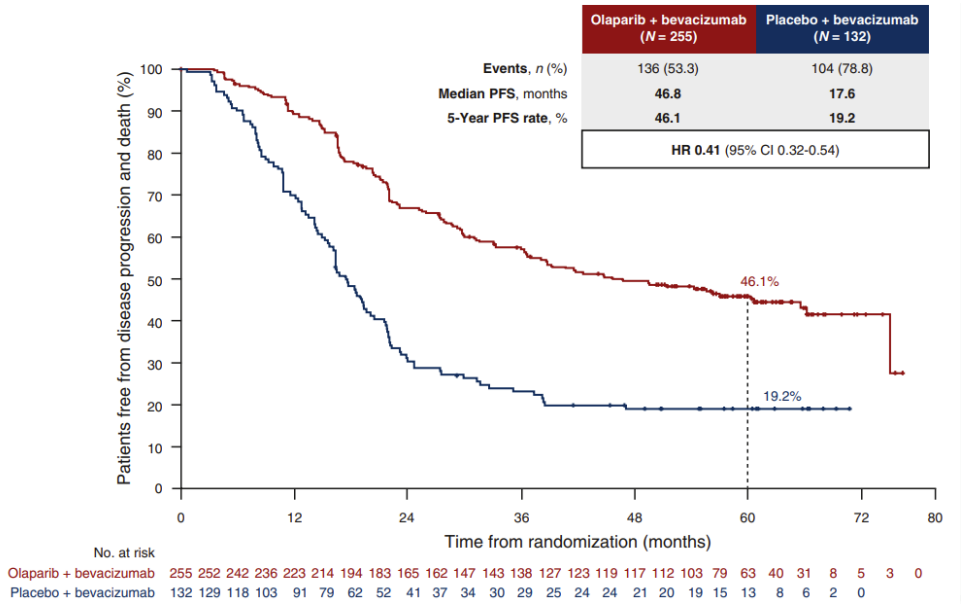
Abbreviations: CI = confidence interval; DCO = data cut-off; HR = hazard ratio; HRD = homologous recombination deficiency; invPFS = investigator-assessed progression-free survival; ITT = intention to treat; PFS2 = progression-free survival to second progression; OS = overall survival

Table 29 Summary of effficacy – PAOLA-1, HRD+ population (used in the MAIC)

	HRD+	
	Olaparib + bevacizumab (n=255)	**Placebo + bevacizumab (n=132)**
invPFS - 22 March 2022 DCO (6)		
Median invPFS, months	46.8 (36.4, 65.7)	17.6 (15.8, 20.3)
HR (95% CI); Log-rank test	0.41 (0.32, 0.54)	
PFS2 - 22 March 2020 DCO (70)		
Median PFS2, months	50.3	35.5
HR (95% CI); Log-rank test	0.56 (0.41, 0.77)	
OS - 22 March 2022 DCO(6)		
Median OS, months	75.2	57.3
HR (95% CI); Log-rank test	0.62 (0.45, 0.85)	

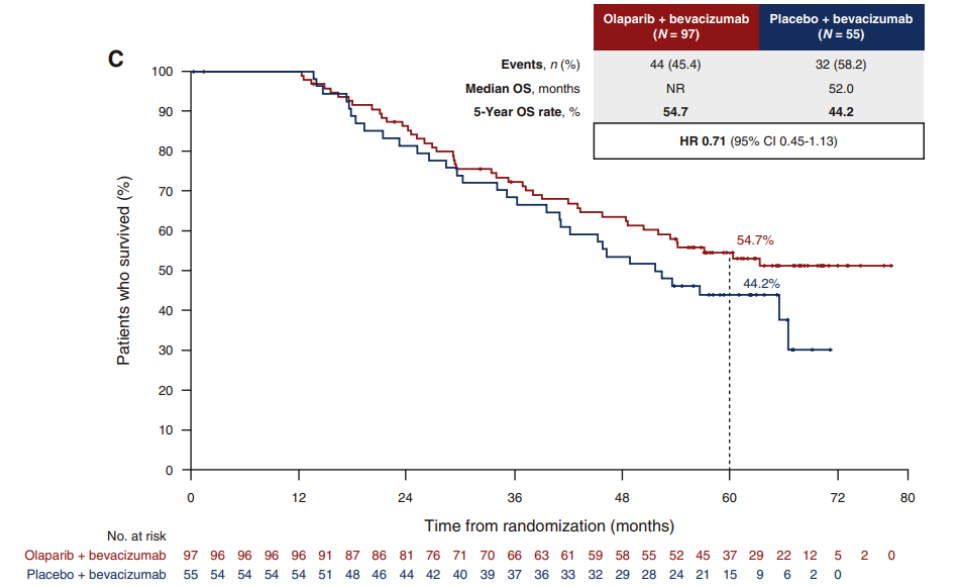
Abbreviations: CI = confidence interval; DCO = data cut-off; HR = hazard ratio; HRD = homologous recombination deficiency; NR = not reached; PFS2 = progression-free survival to second progression; OS = overall survival

Figure 9 PFS KM curve – PAOLA-1(6)



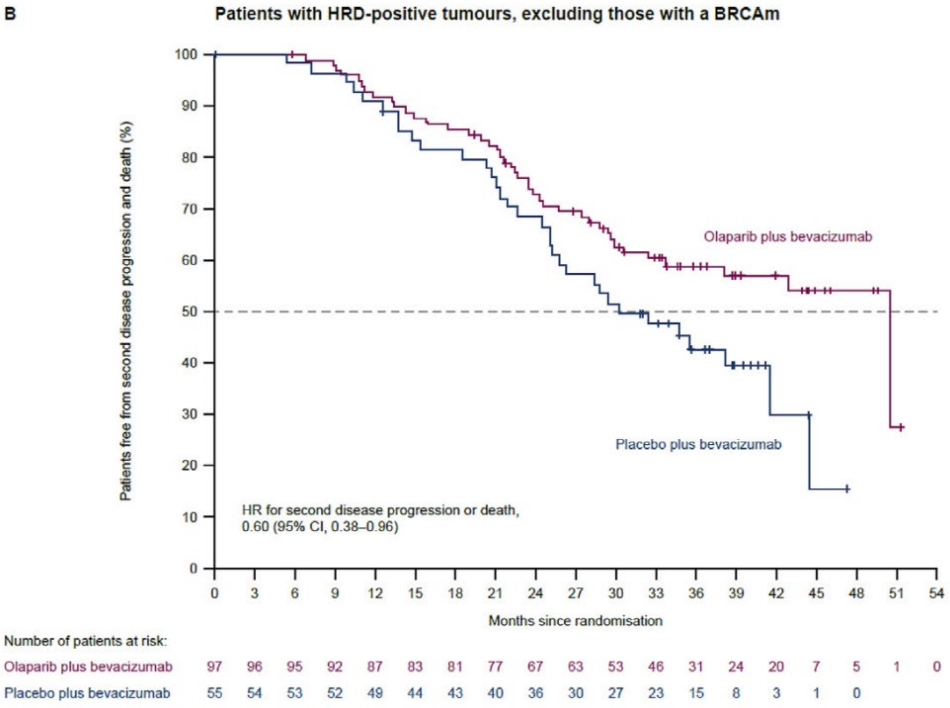
Note: KM curve is for HRD+ patients

Figure 10 OS KM curve – PAOLA-1(6)



Note: KM curve is for non-tBRCA HRD+ patients

Figure 11 PFS2 KM curve – PAOLA-1(70)



Note: KM curve is for non-tBRCA HRD+ patients

7. Comparative analyses of efficacy

7.1 Comparative efficacy of rucaparib vs. niraparib

7.1.1 Differences in definitions of outcomes between studies

There are no relevant differences in how the outcomes are defined in the studies.

7.1.2 Method of synthesis

Following an assessment of data available in PRIMA, a comparison adjusting for all significant effect modifiers was not possible in the non-tBRCA HRD+ population. Therefore, this MAIC is conducted using data from the HRD+ population where all significant effect modifiers can be adjusted for using aggregate data from the PRIMA study.

Since the ATHENA-MONO and PRIMA studies shared the placebo arm as a common control arm, anchored MAICs for invPFS, PFS2, and OS time-to-event outcomes were conducted to assess the comparative efficacy of rucaparib vs. niraparib. The MAIC methodology closely followed the recommendations of the NICE DSU's technical guidelines on population-adjusted indirect comparisons for technology appraisals (TSD18)(93).

The anchored MAIC analysis adjusted for all EMs. More specifically, the following population characteristics were considered as EMs and were used for adjustment in the anchored MAIC.

- Risk class
- ECOG performance score
- FIGO stage
- Receipt of neoadjuvant chemotherapy (NACT)
- Response after chemotherapy
- CA-125 level
- Mutation status (HRD and BRCA).

The PRIMA study population did not include “low-risk” patients fulfilling the three following criteria FIGO stage III or lower, no interval debulking surgery, and successful surgery resulted in complete resection. However, the inclusion/exclusion criteria in the ATHENA-MONO study included patients regardless of their risk classification. Since low vs. high-risk classification as defined by the inclusion criteria in the PRIMA study was considered as an EM, an indicator of risk class was derived for each patient in ATHENA-MONO. This indicator was used for adjustment in the MAIC analysis. Since NACT is administered before interval debulking surgery, NACT and interval debulking surgery are closely related. Given that there is no specific indicator available for neoadjuvant chemotherapy in the ATHENA-MONO dataset, the indicator for interval debulking therapy was used to identify patients who received neoadjuvant chemotherapy. The indirect relative effect of rucaparib vs. niraparib was calculated as the population adjusted HR estimate between rucaparib and placebo arms in ATHENA-MONO divided by the published HR estimate between niraparib and placebo arms in PRIMA.

Individual IPD for invPFS and PFS2 were sourced for rucaparib and placebo arms from the ATHENA-MONO dataset with a DCO date of 17 May 2024, while IPD for OS were taken from the ATHENA-MONO dataset with a DCO date of 09 March 2023. The HR estimates for efficacy outcomes in the PRIMA study cohorts and the related KM curves used for diagnostic procedures were sourced from the published results based on PRIMA dataset with DCO of 08/04/2024(5).

7.1.3 Results from the comparative analysis

Table 30 Results from the comparative analysis of rucaparib vs. niraparib for HRD+ population

Outcome measure	MAIC, HR (95% CI), p-value
invPFS	[redacted]
PFS2	[redacted]
OS	[redacted]

Abbreviation: CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; invPFS, investigator-assessed progression-free survival; MAIC, matching adjusted indirect comparison; OS, overall survival; PFS2, progression-free survival to second progression

7.1.4 Efficacy – results per invPFS

The KM plots including treatment arms in the ATHENA-MONO HRD+ population before and after matching against treatment arms in the PRIMA HRD+ population including adjustment for all available EMs are presented in Figure 12. The PH assumption required for the anchored comparison was tested; the results of these diagnostic procedures are detailed in Appendix C. There was no compelling evidence identified against the PH assumption for any of the outcomes.

Figure 12. Observed and adjusted invPFS KM curves for rucaparib and placebo from ATHENA-MONO vs. niraparib and placebo from PRIMA in the HRD+ population

Notation: Index study, active arm = ATHENA-MONO, rucaparib (DCO: 17/05/2024); Index study, anchor arm = ATHENA-MONO, placebo (DCO: 17/05/2024); Comparator study, active arm = PRIMA, niraparib (DCO: 08 April 2024); Comparator study, anchor arm = PRIMA, placebo (DCO: 08 April 2024)
Abbreviation: invPFS, investigator-assessed progression-free survival; HRD, homologous recombination deficiency; KM, Kaplan-Meier

Table 31 Results for invPFS from the comparative analysis of rucaparib vs. niraparib for HRD+ population

Outcome measure	MAIC, HR (95% CI), p-value
invPFS	[redacted]

Abbreviation: CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; invPFS, investigator-assessed progression-free survival; MAIC, matching adjusted indirect comparison

7.1.5 Efficacy – results per PFS2

KM curves for the PFS2 outcome could not be compared as they were not available for the PRIMA treatment arms.

Table 32 Results for PFS2 from the comparative analysis of rucaparib vs. niraparib for HRD+ population

Outcome measure	MAIC, HR (95% CI), p-value
PFS2	[redacted]

Abbreviation: CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; MAIC, matching adjusted indirect comparison; PFS2, progression-free survival to second progression

7.1.6 Efficacy – results per OS

The KM plots including treatment arms in the ATHENA-MONO HRD+ population before and after matching against treatment arms in the PRIMA HRD+ population including adjustment for all available EMs are presented in Figure 13. The PH assumption required for the anchored comparison was tested; the results of these diagnostic procedures are detailed in Appendix C. There was no compelling evidence identified against the PH assumption for any of the outcomes.

Figure 13. Observed and adjusted OS KM curves for rucaparib and placebo from ATHENA-MONO vs. niraparib and placebo from PRIMA in HRD+ population

Notation: Index study, active arm = ATHENA-MONO, rucaparib (DCO: 09/03/2023); Index study, anchor arm = ATHENA-MONO, placebo (DCO: 09/03/2023); Comparator study, active arm = PRIMA, niraparib (DCO: 08 April 2024); Comparator study, anchor arm = PRIMA, placebo (DCO: 08 April 2024)
Abbreviation: OS, overall survival; HRD, homologous recombination deficiency; KM, Kaplan-Meier

Table 33 Results for OS from the comparative analysis of rucaparib vs. niraparib for HRD+ population

Outcome measure	MAIC, HR (95% CI), p-value
OS	[redacted]

Abbreviation: CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; MAIC, matching adjusted indirect comparison; OS, overall survival

7.2 Comparative efficacy of rucaparib vs. olaparib plus bevacizumab

7.2.1 Differences in definitions of outcomes between studies

There are no relevant differences in how the outcomes are defined in the studies.

7.2.2 Method of synthesis

Following an assessment of data available in PAOLA-1, a comparison adjusting for all significant effect modifiers was not possible in the non-tBRCA HRD+ population. Therefore, this MAIC is conducted using data from the HRD+ population where all significant effect modifiers can be adjusted for using aggregate data from the PAOLA-1 study.

Unanchored MAICs for invPFS, PFS2, and OS were performed to assess the comparative efficacy of rucaparib in ATHENA-MONO vs. olaparib + bevacizumab in PAOLA-1. The MAIC methodology closely followed the recommendations of the National Institute for Health and Care Excellence (NICE) decision support unit's (DSU) technical guidance on the population-adjusted indirect comparisons for technology appraisals (TSD18)(93).

The MAIC analyses adjusted for all key population characteristics that are clinically validated prognostic factors or treatment effect modifiers.

The ATHENA-MONO subgroup analysis showed that prior bevacizumab use might be associated with more favourable treatment effect for rucaparib compared to placebo. However, since only a low proportion (approximately 20%) of the ITT population in ATHENA-MONO received prior bevacizumab and all participants in PAOLA-1 received prior bevacizumab, adjusting for this characteristic would result in a significant reduction in sample size, leading to an insufficient effective sample size (ESS) for the MAIC analysis. Consequently, this variable cannot be adjusted for in the MAIC. Given that not adjusting for bevacizumab use in ATHENA-MONO is in favor of the comparator, the unanchored MAIC approach conducted below is considered as a conservative approach. Furthermore, a difference between ATHENA-MONO and PAOLA-1 was that HRD status was determined prior to randomisation, while HRD status was established post-hoc in PAOLA-1. The following population characteristics were considered for adjustment in the unanchored MAIC of rucaparib versus the olaparib + bevacizumab arms in PAOLA-1:

- Eastern Cooperative Oncology Group (ECOG) performance score

- Tumor location
- International Federation of Gynecology and Obstetrics (FIGO) stage
- Histology
- History of surgery
- Response after chemotherapy
- Cancer antigen 125 (CA-125) level
- Mutation status.

The indirect relative effect of rucaparib vs. the comparators was calculated as the hazard ratio (HR) between the population adjusted outcome for rucaparib in ATHENA-MONO and the reconstructed outcome for the comparator in PAOLA-1 based on published Kaplan-Meier (KM) curves. Individual patient-level data (IPD) for invPFS and PFS2 were sourced from the ATHENA-MONO dataset with a DCO date of 17 May 2024, while IPD for OS were taken from the ATHENA-MONO dataset with a DCO date of 09 March 2023. The outcome data for olaparib + bevacizumab in PAOLA-1 were reconstructed based on the published KM curves in Ray-Coquard et al., 2019(10), Ray-Coquard et al., 2023(6), and González-Martín et al., 2022(70).

7.2.3 Results from the comparative analysis

The relative efficacy estimates from the unanchored MAIC against olaparib + bevacizumab, utilizing all available EMs and PFs for adjustment are presented in Table 34. Across all outcomes, results indicated equivalent efficacy between rucaparib and olaparib plus bevacizumab, with HR values close to 1. It should be noted that the HR estimates reflect the average relative treatment effect over time. In cases where there is evidence of non-proportional hazards, piecewise HRs may more accurately describe the relationship between rucaparib and the comparator. Appendix C includes time dependent HRs before and after 15 months for invPFS and PFS2, respectively.

Table 34 Results from the comparative analysis of rucaparib vs. olaparib plus bevacizumab for HRD+ population

Outcome measure	MAIC, HR (95% CI), p-value
invPFS	[redacted]
PFS2	[redacted]
OS	[redacted]

Abbreviation: CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; invPFS, investigator-assessed progression-free survival; MAIC, matching adjusted indirect comparison; OS, overall survival; PFS2, progression-free survival to second progression

7.2.4 Efficacy – results per invPFS

The KM plots for rucaparib, both before and after MAIC adjustment, as well as for olaparib + bevacizumab, are presented in Figure 14. The PH assumption required for the

unanchored comparison was assessed. The detailed results of these diagnostic procedures are provided in Appendix C. The diagnostics indicated a strong signal for the violation of the PH assumption for invPFS, suggesting that the HR for invPFS may change over time. To address the non-proportional hazards for invPFS, piecewise MAIC analysis was also explored. This approach accounts for time-dependent HRs across different time segments, thereby resolving the PH assumption violations. Results from the piecewise MAIC analyses, assuming a single split point at 15 months, are provided in Appendix C. Multiple split points were not explored further to ensure sufficient data in each time segment for robust estimates.

Figure 14. Observed and adjusted invPFS for rucaparib from the ATHENA-MONO vs. olaparib + bevacizumab from the PAOLA-1 in the HRD+ population

Notation: Index study arm = ATHENA-MONO, rucaparib (DCO: 17/05/2024); Comparator study arm = PAOLA-1, olaparib + bevacizumab (Ray-Coquard et al., 2023; DCO: 22 March 2019)
Abbreviation: invPFS, investigator-assessed progression-free survival; HRD, homologous recombination deficiency; KM, Kaplan-Meier

Table 35 Results for invPFS from the comparative analysis of rucaparib vs. olaparib plus bevacizumab for HRD+ population

Outcome measure	MAIC, HR (95% CI), p-value
invPFS	

Abbreviation: CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; invPFS, investigator-assessed progression-free survival; MAIC, matching adjusted indirect comparison

7.2.5 Efficacy – results per PFS2

The KM plots for rucaparib, both before and after MAIC adjustment, as well as for olaparib + bevacizumab, are presented in Figure 15. The PH assumption required for the unanchored comparison was assessed. The detailed results of these diagnostic procedures are provided in Appendix C. For PFS2, the diagnostics showed a weak signal for the violation of the PH assumption, indicating some potential time-dependence, but not as pronounced as for invPFS. To address the non-proportional hazards for PFS2, piecewise MAIC analysis was also explored. This approach accounts for time-dependent HRs across different time segments, thereby resolving the PH assumption violations. Results from the piecewise MAIC analyses, assuming a single split point at 15 months, are provided in Appendix C. Multiple split points were not explored further to ensure sufficient data in each time segment for robust estimates.

Figure 15. Observed and adjusted PFS2 for rucaparib from the ATHENA-MONO vs. olaparib + bevacizumab from the PAOLA-1 HRD+ population

Notation: Index study arm = ATHENA-MONO, rucaparib (DCO: 17/05/2024); Comparator study arm = PAOLA-1, olaparib + bevacizumab (González-Martín et al., 2022; DCO: 22 March 2020)
Abbreviation: PFS2, progression-free survival to second progression; HRD, homologous recombination deficiency; KM, Kaplan-Meier

Table 36 Results for PFS2 from the comparative analysis of rucaparib vs. olaparib plus bevacizumab for HRD+ population

Outcome measure	MAIC, HR (95% CI), p-value
PFS2	

Abbreviation: CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; MAIC, matching adjusted indirect comparison; PFS2, progression-free survival to second progression

7.2.6 Efficacy – results per OS

The KM plots for rucaparib, both before and after MAIC adjustment, as well as for olaparib + bevacizumab, are presented in Figure 16. The PH assumption required for the unanchored comparison was assessed. The detailed results of these diagnostic procedures are provided in Appendix C. For OS, no compelling evidence was found to suggest a violation of the PH assumption, meaning that the hazard ratios for OS can be considered as constant over time.

Figure 16. Observed and adjusted OS for rucaparib in the ATHENA-MONO HRD-positive cohort vs. olaparib + bevacizumab in the PAOLA-1 HRD-positive cohort

Notation: Index study arm = ATHENA-MONO, rucaparib (DCO: 09/03/2023); Comparator study arm = PAOLA-1, olaparib + bevacizumab (Ray-Coquard et al., 2023; DCO: 22 March 2022)
Abbreviation: OS, overall survival; HRD, homologous recombination deficiency; KM, Kaplan-Meier

Table 37 Results for OS from the comparative analysis of rucaparib vs. olaparib plus bevacizumab for HRD+ population

Outcome measure	MAIC, HR (95% CI), p-value
OS	

Abbreviation: CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; MAIC, matching adjusted indirect comparison; OS, overall survival

8. Modelling of efficacy in the health economic analysis

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

The main source of efficacy data for the rucaparib and routine surveillance arms of the economic model was the ATHENA-MONO trial. TTD was extrapolated using data from the ATHENA-MONO DCO 09 March 2023. Standard parametric distributions including exponential, Weibull, log-normal, log-logistic, Gompertz, and gamma or generalised gamma were applied directly to the rucaparib patient-level data to provide long-term extrapolations. The final choice of extrapolation was made considering the Akaike information criterion (AIC) and Bayesian information criterion (BIC) scores, which determine the relative fit of alternative PSMs to observed data. The AIC and BIC are both reported to assess the models' fit against observed data. A visual inspection vs. the KM estimates was also applied.

8.1.1 Extrapolation of efficacy data

8.1.1.1 Extrapolation of time to treatment discontinuation

Table 38 Summary of assumptions associated with extrapolation of TTD for rucaparib, non-tBRCA HRD+

Method/approach	Description/assumption
Data input	ATHENA-MONO
Model	Standard parametric distributions: Exponential, Weibull, log-normal, log-logistic, Gompertz, generalised gamma, and gamma
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	Standard parametric: exponential
Function with best BIC fit	Standard parametric: exponential
Function with best visual fit	Exponential
Function with best fit according to evaluation of smoothed hazard assumptions	Exponential distribution

Method/approach	Description/assumption
Validation of selected extrapolated curves (external evidence)	Not performed
Function with the best fit according to external evidence	N/A
Selected parametric function in base case analysis	Exponential
Adjustment of background mortality with data from Statistics Denmark	No adjustments performed as death was included as an event in the time-to-discontinuation model.
Adjustment for treatment switching/cross-over	No: N/A
Assumptions of waning effect	No: N/A
Assumptions of cure point	No: N/A

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; HRD = homologous recombination deficiency; KM = Kaplan-Meier; tBRCA = tumour tissue mutation in breast cancer gene; TTD = time to treatment discontinuation

The exponential distribution was selected in the base case for the extrapolation of TTD for rucaparib in the non-tBRCA HRD+ population. In the cost-comparison, the percentage of patient on treatment each month was calculated using the extrapolation with the percentage set to 0% once the maximum treatment duration was reached. Further details are provided in Appendix D.1.

Figure 17 Modelled TTD and KM data for rucaparib, non-tBRCA HRD+

8.1.2 Extrapolation of overall survival

Table 39 Summary of assumptions associated with extrapolation of OS for rucaparib, non-tBRCA HRD+

Method/approach	Description/assumption
Data input	ATHENA-MONO
Model	Standard parametric distributions: exponential, Weibull, log-normal, log-logistic, Gompertz, generalised gamma, and gamma
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	Standard parametric: log-normal
Function with best BIC fit	Standard parametric: log-normal
Function with best visual fit	Log-normal
Function with best fit according to evaluation of smoothed hazard assumptions	Log-normal
Validation of selected extrapolated curves (external evidence)	Validated against HRD/BRCAwt subgroup of PRIMA trial
Function with the best fit according to external evidence	Log-normal
Selected parametric function in base case analysis	Log-normal
Adjustment of background mortality with data from Statistics Denmark	No additional adjustment for background mortality was performed as deaths occuring in the extrapolated models far exceeded those in the general population within the time horizon of the model.
Adjustment for treatment switching/cross-over	No: N/A
Assumptions of waning effect	No: N/A
Assumptions of cure point	None

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; HRD = homologous recombination deficiency; KM = Kaplan-Meier; PFS2 = progression-free survival to second progression; tBRCA = tumour tissue mutation in breast cancer gene

Figure 18 Modelled and KM data for rucaparib overall survival (OS), non-tBRCA HRD+

Abbreviations: HRD = homologous recombination deficiency; KM = Kaplan-Meier; OS = overall survival; tBRCA = tumour tissue mutation in breast cancer gene

8.1.3 Calculation of transition probabilities

Table 40 Transitions in the health economic model

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

8.2 Presentation of efficacy data from [additional documentation]

Not applicable.

8.3 Modelling effects of subsequent treatments

Not applicable.

8.4 Other assumptions regarding efficacy in the model

Not applicable.

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

Table 41 Estimates in the model (N/A)

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
N/A	N/A	N/A	N/A

In Table 41 please provide the modelled average treatment length and time in model health state and describe any assumptions used to derive these.]

Maximum treatment duration as per treatment guidelines and average treatment duration as reported in respective clinical trials are presented in Table 41.

Table 42 Overview of modelled average treatment length and time in model health state, undiscounted and adjusted for half cycle correction

Treatment	Treatment length [months]	Health state 1 [months]
Rucaparib	Max treatment duration: 24 months(1) Modelled average time-to-treatment discontinuation: [redacted] years	N/A
Niraparib	Max treatment duration: 36 months(9) Data on time-to-treatment discontinuation not available. In line with assumption of comparable efficacy between rucaparib and niraparib, extrapolated time-to-treatment discontinuation was used for niraparib. Modelled average time on treatment: [redacted] years	N/A

9. Safety

9.1 Safety data from the clinical documentation

All patients who received at least one dose of rucaparib (n=425) or placebo (n=110) were included in the ATHENA-MONO safety analysis.(7) Safety was assessed from the first administration of study drug until 28 days after the last dose of oral drug.(7) At the 23 March 2022 DCO, median treatment duration was 14.7 (range: 0.1, 32.7) months in the rucaparib group and 9.9 (range: 0.9, 25.9) months in the placebo group.(7) Median dose intensity was 0.88 (IQR: 0.680, 0.995) in the rucaparib group and 1.00 (IQR: 0.970, 1.000) in the placebo group.(7) The final safety analysis for ATHENA-MONO was conducted on 9 March 2023.(8) However, the 23 March 2022 DCO has been used in the model because

the follow-up duration is the most comparable with data available for PRIMA and PAOLA-1.

Safety outcomes in PRIMA were evaluated in all patients who received one or more doses of niraparib (n=484) or placebo (n=244).(54) At the 17 May 2019 DCO, median treatment duration was not reported in either treatment group.(54) In the overall study population treated with niraparib, 16.3% of patients had an AE leading to discontinuation.(5) Safety data at 3.5 years follow up (17 November 2021 DCO) is also available for PRIMA.(89) However, the 17 May 2019 DCO has been used in the model because the follow-up duration is the most comparable with data available for ATHENA-MONO and PAOLA-1.

Safety outcomes in PAOLA-1 were evaluated in all patients who received one or more doses of olaparib plus bevacizumab (n=535) or placebo plus bevacizumab (n=267).(10) At the 22 March 2019 DCO, median treatment duration was 11.0 months (range: 0.7, 21.4) in the olaparib plus bevacizumab group and 10.6 months (range: 0.7, 17.1) in the placebo plus bevacizumab group.(10)

The overall safety events and SAEs for the ATHENA-MONO, PRIMA and PAOLA-1 studies are presented in Table 42 and Table 43, respectively. None of the studies reported the difference (% [95% CI]) between treatment and comparator. None of the studies reported number of SAEs.

Table 43 Overview of safety events in the safety populations of ATHENA-MONO, PRIMA and PAOLA-1

	ATHENA-MONO (23 March 2022 DCO)(7, 27, 42)			PRIMA (17 May 2019)(54)		PAOLA-1 (22 March 2019 DCO)(10)	
	Rucaparib (n=425)	Placebo (n=110)	Difference, % (95 % CI)	Niraparib (n=484)	Placebo (n=244)	Olaparib plus bevacizumab (n=535)	Placebo plus bevacizumab (n=267)
Number of adverse events, n	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Number and proportion of patients with ≥1 adverse events, n (%)	411 (96.7%)	102 (92.7%)	Not reported	478 (98.8%)	224 (91.8%)	531 (99%)	256 (96%)
Number of serious adverse events, n	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Number and proportion of patients with ≥ 1 serious adverse events, n (%)	90 (21.2%)	7 (6.4%)	Not reported	156 (32.2%)	32 (13.1%)	167 (31%)	83 (31%)
Number of CTCAE grade ≥3 events, n	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Number and proportion of patients with ≥1 CTCAE grade ≥ 3 events, n (%)	257 (60.5%)	25 (22.7%)	Not reported	341 (70.5%)	46 (18.9%)	303 (57%)	136 (51%)
Number of adverse reactions, n	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

	ATHENA-MONO (23 March 2022 DCO)(7, 27, 42)			PRIMA (17 May 2019)(54)		PAOLA-1 (22 March 2019 DCO)(10)	
	Rucaparib (n=425)	Placebo (n=110)	Difference, % (95 % CI)	Niraparib (n=484)	Placebo (n=244)	Olaparib plus bevacizumab (n=535)	Placebo plus bevacizumab (n=267)
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	391 (92.0%)	75 (68.2%)	Not reported	466 (96.3%)	168 (68.9%)	Not reported	Not reported
Number and proportion of patients who had a dose reduction due to adverse events, n (%)	210 (49.4%)	9 (8.2%)	Not reported	343 (70.9%)	20 (8.2%)	220 (41%)	20 (7%)
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	271 (63.8%)	89 (80.9%)	Not reported	307 (63.4%)	175 (71.7%)	331 (61.9%)	194 (72.7%)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	50 (11.8%)	6 (5.5%)	Not reported	58 (12.0%)	6 (2.5%)	109 (20%)	15 (6%)

Abbreviations: CI = confidence interval; CTCAE = Common Terminology Criteria for Adverse Events; DCO = data cut-off

Table 44 Number and % of patients with serious adverse events with frequency of ≥1% in any trial arm

	ATHENA-MONO (23 March 2022 DCO)(27, 42)		PRIMA (17 May 2019)(54)		PAOLA-1 (22 March 2019 DCO)(10)	
Adverse events	**Rucaparib (n=425)**	**Placebo (n=110)**	**Niraparib (n=484)**	**Placebo (n=244)**	**Olaparib plus bevacizumab (n=535)**	**Placebo plus bevacizumab (n=267)**
Any serious adverse event	90 (21.2%)	7 (6.4%)	156 (32.2%)	32 (13.1%)	167 (31.2%)	83 (31.1%)
Any treatment-related serious adverse event	34 (8.0%)	1 (0.9%)	118 (24.4%)	6 (2.5%)	Not reported	Not reported
Anaemia	17 (4.0%)	0	Not reported	Not reported	34 (6.4%)	1 (0.4%)
Neutropenia	6 (1.4%)	0	Not reported	Not reported	5 (0.9%)	1 (0.4%)
Thrombocytopenia / platelet count decreased	5 (1.2%)	0	Not reported	Not reported	4 (0.7%)	1 (0.4%)
Hypertension	[redacted]	[redacted]	Not reported	Not reported	48 (9.0%)	35 (13.1%)
Intestinal obstruction	3 (0.7%)	0	Not reported	Not reported	16 (3.0%)	5 (1.9%)
Pulmonary embolism	[redacted]	[redacted]	Not reported	Not reported	8 (1.5%)	1 (0.4%)

	ATHENA-MONO (23 March 2022 DCO)(27, 42)		PRIMA (17 May 2019)(54)		PAOLA-1 (22 March 2019 DCO)(10)	
Adverse events	**Rucaparib (n=425)**	**Placebo (n=110)**	**Niraparib (n=484)**	**Placebo (n=244)**	**Olaparib plus bevacizumab (n=535)**	**Placebo plus bevacizumab (n=267)**
Myocardial infarction	[redacted]	[redacted]	Not reported	Not reported	0	5 (1.9%)

Abbreviation: DCO = data cut-off

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

This section is not applicable since a cost comparison is presented in the current application and no AEs were included in the analysis.

Table 45 Adverse events used in the health economic model

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Adverse event, n (%)	N/A	N/A	N/A	N/A

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

A cost comparison is performed in this application. The focus of this section is on comparing the intervention and comparators' effect on HRQoL measured in the studies (Table 45).

In the ATHENA-MONO trial, HRQoL was assessed using the Functional Assessment of Cancer Therapy-Ovarian Trial Outcome Index and EQ-5D-5L(7, 27). Results for FACT-O TOI, FOSI, and EORTC QLQ-OV28 for the PRIMA study were reported on clinicaltrials.gov(85).

Table 46 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	ATHENA-MONO(27)	Description of HRQoL results for rucaparib.
FACT-O TOI	ATHENA-MONO(7, 27)	Description of HRQoL results for rucaparib.
EORTC QLQ-C30	PAOLA-1(10), PRIMA(85)	Description of HRQoL results for niraparib and olaparib in combination with bevacizumab.
FOSI	PRIMA(85)	Description of HRQoL results for niraparib.
EORTC QLQ-OV28	PRIMA(85)	Description of HRQoL results for niraparib.

Abbreviation: HRQoL = health-related quality of life, FACT-O TOI = functional assessment of cancer therapy – Ovarian Trial Outcome Index, EORTC QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, FOSI = Ovarian Symptom Index

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

10.1.1 Study design and measuring instrument

PROs assessed using the EQ-5D-5L was an exploratory efficacy objective in the ATHENA-MONO study.(27) Patients completed the EQ-5D-5L on an electronic device or other format (i.e., paper form) before any other scheduled study procedures were performed and dosing occurred (if applicable).(27)

10.1.2 Data collection

EQ-5D-5L was assessed at Screening, on Day 1 (Cycle 1 through 3, and Cycle 5), then every 12 weeks (aligning with computed tomography scans) until treatment discontinuation or until the visit cut-off date for the primary analysis, whichever came first.(27) In addition, EQ-5D-5L assessments were performed at end of treatment, and at the 28-day safety follow-up and the 5-month safety follow-up for all patients.(27)

Patients who did not have both a baseline measurement and at least 1 post-baseline measurement were excluded.(27) At a given visit, the change from baseline was analysed for the treatment comparisons using an ANCOVA with treatment and stratification variables as categorical factors and baseline measurement for the parameter as a continuous covariate.(27)

The completion rates for EQ-5D-5L using either electronic or paper questionnaires were approximately 90% in both the rucaparib and placebo groups for the first 12 months of treatment (23 March 2022 DCO; Table 46).(27)

Table 47 Pattern of missing data and completion in ATHENA-MONO as of 23 March 2022(27)

	Rucaparib (n=427)				Placebo (n=111)			
Time point	HRQoL population, N	Missing, n (%)	Expected to complete, n	Completion, n (%)	HRQoL population, N	Missing, n (%)	Expected to complete, n	Completion, n (%)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 8 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 11 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 14 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Rucaparib (n=427)				Placebo (n=111)			
Time point	HRQoL population, N	Missing, n (%)	Expected to complete, n	Completion, n (%)	HRQoL population, N	Missing, n (%)	Expected to complete, n	Completion, n (%)
Cycle 17 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 20 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 23 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 26 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 29 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 32 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 35 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: HRQoL = health-related quality of life

10.1.3 HRQoL results – EQ-5D-5L Index Value (UK)

There were no statistically significant or clinically meaningful differences in PROs between study groups, suggesting that rucaparib maintenance treatment improved efficacy outcomes over placebo without negatively impacting HRQoL (Table 49).(7, 27)

Table 48 HRQoL EQ-5D-5L Index Value (UK) summary statistics in ATHENA-MONO as of 23 March 2022(27)

	Rucaparib (n=427)		Placebo (n=111)		Rucaparib vs. placebo	Difference from placebo
	N	Mean (SD)	N	Mean (SD)		p-value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Cycle 2 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 8 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 11 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 14 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 17 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 20 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 23 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 26 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Last on-treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HRQoL = health-related quality of life; SD = standard deviation; UK = United Kingdom

10.2 Presentation of health-related quality of life FACT-O-TOI

10.2.1 Study design and measuring instrument

PROs assessed using the FACT-O was an exploratory efficacy objective in the ATHENA-MONO study.(27) Patients completed the FACT-O on an electronic device or other

format (i.e., paper form) before any other scheduled study procedures were performed and dosing occurred (if applicable).(27)

The FACT-O TOI is a condensed scoring subset of the FACT-O which combines scores from three domains: Physical Well-Being, Functional Well-Being, and the Ovarian Cancer Subscale, totaling 26 items out of the full 39-item FACT-O questionnaire(7).

10.2.2 Data collection

FACT-O TOI was assessed at Screening, on Day 1 (Cycle 1 through 3, and Cycle 5), then every 12 weeks (aligning with computed tomography scans) until treatment discontinuation or until the visit cut-off date for the primary analysis, whichever came first.(27) In addition, FACT-O TOI assessments were performed at end of treatment, and at the 28-day safety follow-up and the 5-month safety follow-up for all patients.(27)

Analyses of changes from baseline were analysed for each scheduled post-baseline visit and for the final visit. Patients that did not have both a baseline measurement and at least 1 post-baseline measurement were not included. At a given visit, the change from baseline was analysed for the treatment comparisons using an ANCOVA with treatment and stratification variable as a categorical factors and baseline measurement for the parameter as a continuous covariate. A change of at least 10 points in the FACT-O TOI was considered as clinically relevant and minimally important difference and was summarized categorically.

The completion rates for FACT-O using either electronic or paper questionnaires were approximately 90% in both the rucaparib and placebo groups for the first 12 months of treatment (23 March 2022 DCO; Table 48).(27)

Table 49 Pattern of missing data and completion for FACT-O

	Rucaparib (n = 427)			Placebo (n = 111)		
Time point	Missing N (%)	Expected to complete N	Completion N (%)	Missing N (%)	Expected to complete N	Completion N (%)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 8 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 11 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 14 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 17 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 20 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 23 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Rucaparib (n = 427)			Placebo (n = 111)		
Time point	Missing N (%)	Expected to complete N	Completion N (%)	Missing N (%)	Expected to complete N	Completion N (%)
Cycle 26 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 29 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 32 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 35 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

10.2.3 HRQoL results

Results for the FACT-O TOI are summarised in Figure 17 and Table 49 for the ITT population of the ATHENA-MONO study(7, 27). There were no differences in the FACT-O TOI score between the rucaparib and placebo arm across all time points.

Figure 19 Change from baseline in FACT-O TOI score (ITT)

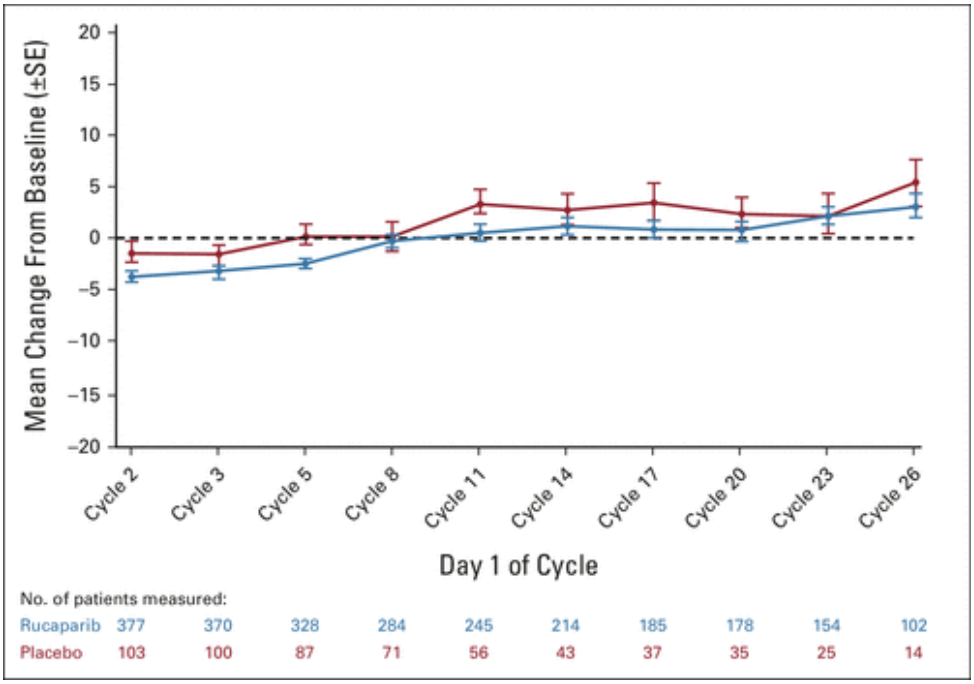


Table 50 HRQoL FACT-O TOI summary statistics (ITT)

	Intervention (rucaparib)		Comparator (placebo)		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline					
Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Intervention (rucaparib)		Comparator (placebo)		Intervention vs. comparator
Cycle 11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Last On-treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

10.3 Presentation of health-related quality of life EORTC QLQ-C30

In PRIMA and PAOLA-1, EORTC QLQ-C30 were reported. Only results for the mean global health status – quality of life score was reported in PAOLA-1 and included the mean change from baseline and estimated between-group difference(10). For the PRIMA study, the change from baseline and SE were reported, with no between-group comparison(85).

In both studies, results were reported for the full study population (ITT), which is broader than the indication relevant for this submission.

10.3.1 Study design and measuring instrument

The EORTC QLQ-C30 is a cancer-specific questionnaire assessing 15 health-related quality of life (HRQoL) scales through 30-items: a global health status, five functional scales (physical, role, emotional, cognitive, and social) and nine symptomatic scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). For each dimension, one score is generated on a 0–100 scale, with higher score representing better HRQoL. For the global health status dimension of the EORTC QLQ-C30 questionnaire, a difference of 10 points is considered a minimally clinically important difference(10).

10.3.2 Data collection

In PAOLA-1, EORTC QLQ-C30 assessment was performed by the subjects at baseline and then every 12 weeks until second disease progression (PFS2)(10). In the PRIMA study, EORTC QLQ-C30 assessment was performed very 8 weeks for 56 weeks, then every 12

weeks while on study treatment(54). Patterns of missing data and completion were not available for the PAOLA-1 and PRIMA studies.

Table 51 Pattern of missing data and completion

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)
NR	NR	NR	NR	NR

Abbreviation: NR, not reported

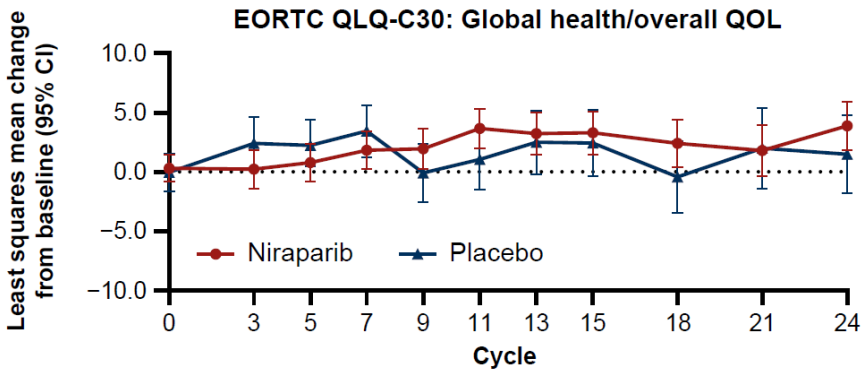
10.3.3 HRQoL results

EORTC QLQ-C30 results available for the PAOLA-1 and PRIMA studies are limited. Results were available for a single time point and only for the overall population included in the respective trials, which is broader than the population relevant for this submission.

Table 52 HRQoL EORTC QLQ-C30 summary statistics – PRIMA study(85)

	Intervention (niraparib)		Comparator (placebo)		Intervention vs. comparator
Global Health Status	N	Change from baseline Mean (SE)	N	Change from baseline Mean (SE)	Difference (95% CI) p-value
Week 24	478	1.009 (0.6898)	243	1.177 (1.0005)	Not reported

Figure 20 HRQoL EORTC QLQ-C30 Global Health Score - PRIMA (ITT)(5)



Niraparib, *n*	478	427	359	322	289	256	236	212	176	158	141
Niraparib mean score	71.5	72.3	73.5	74.7	75.1	77.5	76.9	77.4	76.9	76.9	78.8
Placebo, *n*	243	229	187	161	126	102	96	81	71	61	51
Placebo mean score	70.2	73.9	74.6	76.4	72.2	74.8	75.8	77.0	73.6	74.3	74.5

Table 53 HRQoL EORTC QLQ-C30 summary statistics – PAOLA-1 study(54)

	Intervention (olaparib plus bevacizumab)		Comparator (bevacizumab plus placebo)		Intervention vs. comparator
Global Health Status	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline		68.6		37.1	Not reported
Week 24 Change from baseline	498	-1.33 (95% CI, -2.47 to -0.19)	246	-2.89 (95% CI, -4.52 to -1.26)	1,56 (95% CI, -0.42 to 3.55)

10.4 Presentation of health-related quality of life FOSI

10.4.1 Study design and measuring instrument

The FOSI (Functional Assessment of Cancer Therapy – Ovarian Symptom Index) is an 8-item patient-reported outcome measure designed to assess symptom response in women with ovarian cancer. It is derived from the longer FACT-O and focuses on key symptoms such as pain, nausea, vomiting, lack of energy, abdominal swelling and cramps, as well as emotional concerns like worry about disease progression and overall life satisfaction. Each item uses a 5-point Likert scale reflecting experiences over the past 7 days, and scores are manually calculated, with some items reverse-scored(85).

10.4.2 Data collection

In the PRIMA study, FOSI assessment was performed very 8 weeks for 56 weeks, then every 12 weeks while on study treatment. Patterns of missing data and completion were not available for the PRIMA study(54).

10.4.3 HRQoL results

FOSI results available for the PRIMA studies are limited. Results were available for a single time point and only for the overall population included in the trials, which is broader than the population relevant for this submission.

Table 54 HRQoL FOSI summary statistics – PRIMA study(85)

	Intervention (niraparib)		Comparator (placebo)		Intervention vs. comparator
	N	Change from baseline Mean (SE)	N	Change from baseline Mean (SE)	Difference (95% CI) p-value
Week 24	479	-0.4 (0.15)	240	-0.3 (0.22)	Not reported

10.5 Presentation of health-related quality of life EORTC QLQ-OV28

10.5.1 Study design and measuring instrument

The EORTC QLQ-OV28 is a validated ovarian cancer-specific module designed to complement the EORTC QLQ-C30 in assessing health-related quality of life in women with ovarian cancer. It contains 28 items grouped into several domains: abdominal/gastrointestinal symptoms, chemotherapy side effects, hormonal symptoms, body image, sexual functioning, treatment-related burden, and future health concerns. Responses are scored on a four-point Likert scale and transformed to a 0–100 scale, with higher scores indicating greater symptom severity or impact(54).

10.5.2 Data collection

In the PRIMA study, EORTC QLQ-OV28 assessment was performed very 8 weeks for 56 weeks, then every 12 weeks while on study treatment. Patterns of missing data and completion were not available for the PRIMA study(54).

10.5.3 HRQoL results

EORTC QLQ-OV28 results available for the PRIMA studies are limited. Results were available for a single time point and only for the overall population included in the trials, which is broader than the population relevant for this submission.

Table 55 HRQoL EORTC QLQ-OV28 summary statistics – PRIMA study(85)

	Intervention (niraparib)		Comparator (placebo)		Intervention vs. comparator
Up to 34 months	N	Change from baseline Mean (SE)	N	Change from baseline Mean (SE)	Difference (95% CI) p-value
<u>Functional scale:</u>					
Body image	475	8.49 (1.014)	244	10.07 (1.482)	Not reported
Sexuality	471	3.63 (0.800)	240	3.26 (1.189)	Not reported
Attitude to disease/treatment	475	13.66 (0.931)	244	12.22 (1.326)	Not reported
<u>Symptom scale:</u>					
Abdominal/GI	481	2.19 (0.57)	244	0.83 (0.811)	Not reported
Peripheral neuropathy	480	-8.22 (0.930)	244	-9.64 (1.322)	Not reported
Hormonal/menopause symptoms	480	1.50 (0.880)	244	-2.52 (1.307)	Not reported
Other chemo side effects	480	-2.22 (0.558)	244	-3.02 (0.836)	Not reported
Hair loss	477	-23.36 (0.982)	242	-20.74 (1.369)	Not reported

10.6 Health state utility values (HSUVs) used in the health economic model (N/A)

A cost comparison is carried out in this application; this section is not applicable.

10.6.1 HSUV calculation

Not applicable.

10.6.1.1 Mapping

Not applicable.

10.6.2 Disutility calculation

Not applicable.

10.6.3 HSUV results

Not applicable

Table 56 Overview of health state utility values [and disutilities] (N/A)

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

10.7 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy (N/A)

A cost comparison is carried out in this application; this section is not applicable.

10.7.1 Study design

Not applicable.

10.7.2 Data collection

Not applicable.

10.7.3 HRQoL Results

Not applicable.

10.7.4 HSUV and disutility results

Not applicable.

Table 57 Overview of health state utility values [and disutilities] (N/A)

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

Table 58 Overview of literature-based health state utility values (N/A)

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

11. Resource use and associated costs

11.1 Medicines - intervention and comparator

The economic analysis compares the treatment costs, administration costs, and patient time costs of the rucaparib and niraparib. In the base case, the dose of rucaparib was based on the dose as per label; in the case of niraparib, the dose was based on individual starting dose criteria. Treatment duration was based on the extrapolation of time to discontinuation using data from the ATHENA-MONO study, using 24 and 36 months maximum treatment duration for rucaparib and niraparib, respectively.

Table 59 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Rucaparib	600mg	82.0%	Twice daily	N/A (oral)
Niraparib	200 or 300mg	62.6% (181.3mg)	Once daily	N/A (oral)

Table 60. Applicant's analysis: Modeled average treatment durations for the individual drugs, non-discounted estimates (half-cycle corrected and corrected for background mortality)

	Duration in months	Duration in years	Stoppig rule in the model
Rucaparib (extrapolation model)	[redacted]	[redacted]	2 years (24 months)

	Duration in months	Duration in years	Stoppig rule in the model
Niraparib (extrapolation model):	[redacted]	[redacted]	3 years (36 months)

11.2 Medicines– co-administration

No relevant co-administration, this section is not applicable.

11.3 Administration costs

Oral therapies rucaparib and niraparib are assumed to have no administration cost. For subsequent treatments, infusion drugs are assumed to have an administration cost on each day of administration, according to the duration of administration using tariff for DRG 13MA98, (i.e. MDC13 1-dagsgruppe, pat. Mindst 7 år) for the cost of chemotherapy administration.(87) MDC 13 applies to Diseases and Disorders of the Female Reproductive System in ICD-10 and dagsgruppe represent ambulant care, as chemotherapy is administered in the outpatient setting. The administration costs used in model are summarised in Table 61.

Table 61 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Oral administration	N/A	0	N/A	
Infusion (subsequent treatment)	As per label	1,411.00	13MA98	DRG 2025(87)

11.4 Disease management costs

Disease management costs include monitoring visits scheduled monthly for all treatments. Additionally, for niraparib, weekly visits are advised in the first month of treatment, resulting in an extra 3 monitoring visits across the follow-up period.

Table 62 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Specialist visit	Monthly	1411	13MA09	DRG 2025(87)
Monitoring visit	Niraparib: weekly monitoring during	1411	13MA09	DRG 2025(87)

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
	first month of treatment			

Table 63. Applicant's analysis: Assumptions regarding costs for treatment monitoring

Course	Frequency	Duration	Diagnosis and procedure codes*	DRG group	Unit costs (DKK)
Oncologist visit (rucaparib or niraparib treatment)	Every 4 weeks	Until treatment discontinuation	MDC131	13MA09 - MDC131-dagsgruppe, pat.mindst 7 ar	1,411
Additional monitoring visit on first month of niraparib treatment	Every week (3 additional visits)	In the first month of niraparib treatments	MDC131	13MA09 - MDC131-dagsgruppe, pat.mindst 7 ar	1,411

*include other patient information if relevant for the selection of DRG group; A = action diagnosis; P = procedure.

11.5 Costs associated with management of adverse events

Not applicable as costs associated with management of adverse events are assumed equal between the treatment options considered in the cost comparison.

Table 64 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
N/A	N/A	N/A

11.6 Subsequent treatment costs

Within ATHENA, some patients on rucaparib received PARPs as subsequent treatment. However, PARPi after PARPi is not currently allowed within Danish clinical practice, therefore subsequent treatment with PARP inhibitors was not included in the subsequent treatment costs for patients treated with rucaparib or niraparib maintenance.

The distributions of non-PARPi subsequent treatments were informed by clinical expert opinion through consultation with an oncologist in Denmark. It was assumed that the distribution of non-PARPi subsequent treatments is similar for rucaparib and niraparib, which was confirmed by the clinical expert opinion.

Duration of treatment with bevacizumab and gemcitabine was based on previous Ola/Bev submission.(46) Durations of treatment for carboplatin, paclitaxel, and PLDH were based on the NICE appraisal for rucaparib 1L maintenance in aOC(94). Treatment duration for cisplatin was assumed to be the same as for carboplatin (5 months).

Table 65 Subsequent therapies assumptions applied per year in the model

	All treatments	
Therapy	**Proportion**	**Duration of treatment (Months)**
No subsequent therapy	[redacted]	[redacted]
Carboplatin or cisplatin	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
PLDH	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]

Abbreviation: PLDH = pegylated liposomal doxorubicin Source: Denmark KOL

The subsequent medical treatments, doses, RDI, and administration frequencies are summarised in Table 63.

Table 66 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing	Route of administration	Length of administration (minutes)
Carboplatin	400 mg/m2	100%	Every 3 weeks	yes	IV	30
Gemcitabine	1000 mg/m2	100%	Twice every 3 weeks	yes	IV	30
Paclitaxel	175 mg/m2	100%	Every 3 weeks	yes	IV	180
PLDH	50 mg/m2	100%	Every 4 weeks	yes	IV	75
Bevacizumab	15 mg/kg	100%	Every 3 weeks	yes	IV	48.54

The daily subsequent therapy cost was then calculated based on dose per admin, number of administration, and route of administration (Table 59). Assumptions for weight and body surface area were 68.6kg (PRIMA baseline)(32) and 1.71 m^2 (95), respectively. In addition, costs for an oncologist visit, patient time and transport costs, for each three-weekly visit is included using the same calculations as for initial

maintenance therapy. Overall annualised costs were converted into a monthly cost applied following discontinuation from initial maintenance therapy. The resulting monthly cost of subsequent therapy applied for 1 year following discontinuation was DKK34,737.01.

Table 67. Applicant's analysis: Assumptions regarding subsequent treatment

Subsequent treatment	Rucaparib [x % e.g. progressed patients]	Niraparib [x % e.g. progressed patients]	Average treatment duration [source]	Dosage (Dose and administration route)	Any assumptions regarding dose adjustment and pause, incl. sources
No subsequent therapy	XXXX	XXXX	N/A		
Carboplatin	XXXX	XXXX	5 months (EMA Summary of Product Characteristics: Carboplatin)	400 mg/m2, every 3 weeks, IV administration	No additional assumptions
Gemcitabine	XXXX	XXXX	4 months (EMA Summary of Product Characteristics: Gemcitabine)	1000 mg/m2, twice every 3 weeks, IV administration	No additional assumptions
Paclitaxel	XXXX	XXXX	5 months (EMA Summary of Product Characteristics: Paclitaxel)	175 mg/m2, every 3 weeks, IV administration	No additional assumptions
PLDH	XXXX	XXXX	3 months (EMA Summary of Product Characteristics: PLDH)	50 mg/m2, every 4 weeks, IV administration	No additional assumptions
Bevacizumab	XXXX	XXXX	11.7 months (DGCG guidelines; https://www.dgcg.dk/images/retningslinier/Ovariecancer/Hndtering%20af%20medicinsk%20behandling%20ved%20avanceret%20epithelial%20ov	15 mg/kg, every 3 weeks, IV administration	No additional assumptions

Subsequent treatment	Rucaparib [x % e.g. progressed patients]	Niraparib [x % e.g. progressed patients]	Average treatment duration [source]	Dosage (Dose and administration route)	Any assumptions regarding dose adjustment and pause, incl. sources
			ariecancer_14.06.24_DGCG.pdf)		

11.7 Patient costs

For infusions on bevacizumab during subsequent therapy, patient time costs was considered as follows in line with the EMA SPC: “First infusion, 90 minutes, second infusion, 60 minutes, subsequent infusion 45 minutes (based on 50% tolerating a reduction to 30 minutes and the remainder requiring 60 minute infusion)”(11).

To calculate the average patient time to apply in the cost comparison, the overall patient time cost over 11.7 months of treatment was calculated as a per day cost at 188 DKK/hour based on Medicinradet guidelines. 11.7 months treatment equated to 16.95 infusions which based on infusion time assumptions resulted in an average of 48.54 minutes per infusion.

Patient and transport costs related to specialist or monitoring visits were calculated based on 20km one-way travel to hospital at DKK3.79/km based on Medicinradet guidelines. Transport time was 80 minutes and 20 minutes of consultation time.

Table 68 Patient costs used in the model

Activity	Time spent [minutes, hours, days]	Cost (patient time and transport)
Bevacizumab infusion	[90 + 60 +((30*0.5) + (60*0.5))*(16.95-2)] / 16.95 = 48.54 minutes average per infusion	48.54 min x 188/hour = DKK152.09
Specialist or monitoring visit	40 km travel + 80 minutes travel time + 20 minutes consultation time	100 min x 188/hour + 40km x 3.79/km = 313.33 + 151.60 = 464.93

Table 69. Applicant's assumptions regarding patient time consumption

Activity	Frequency of activity	Patient's time consumption on activity	Patient's transport time	Note
Oncologist visit (rucaparib or niraparib treatment)	Every 4 weeks whilst on treatment (based on TTD extrapolation)	20 min	100 min	
Additional monitoring visit on first month of niraparib treatment	Every week (3 additional visits)	20 min	100 min	
Onologist visit (subsequent treatment)	Every 3 weeks for 1 year	20 min	100 min	
Intravenous administration of carboplatin	Every 3 weeks for 5 months	30 minutes	0	No separate transport time (as it takes place during oncologist visit)
Intravenous administration of gemcitabine	2 times every 3 weeks for 4 months	30 minutes	0	No separate transport time (as it takes place during oncologist visit)
Intravenous administration of paclitaxel	Every 3 weeks for 5 months	180 minutes	0	No separate transport time (as it takes place during oncologist visit)
Intravenous administration of PLDH	Every 3 weeks for 3 months	75 minutes	0	No separate transport time (as it takes place during oncologist visit)
Intravenous administration of bevacizumab	Every 3 weeks for 11.7 months	48.54 minutes	0	No separate transport time (as it takes place during oncologist visit)

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

Not applicable as palliative care costs are assumed equal between the treatment options considered in the cost comparison

12. Results

12.1 Base case overview

The health economic analysis is based on a cost comparison between rucaparib and niraparib or olaparib in combination with bevacizumab. An overview of the base case is presented in Table 65.

Table 70 Base case overview

Feature	Description
Comparator	Niraparib
Type of model	Cost comparison
Time horizon	4 years
Treatment line	1L maintenance and subsequent treatment post-discontinuation
Measurement and valuation of health effects	Not applicable
Costs included	Medicine costs Administration costs Monitoring costs Patient and transport costs Subsequent treatment costs
Dosage of medicine	Rucaparib: Fixed dose for rucaparib multiplied by respective RDI (%). Niraparib: Median dose intensity (mg/day) reported in the PRIMA study
Average time on treatment	Treatment duration is calculated based on available TTD (time-to-treatment discontinuation) data for rucaparib (ATHENA-MONO) and niraparib (PRIMA). TTD was not available for niraparib (PRIMA) from publications and was redacted within previous HTA

Feature	Description
	submissions, therefore the TTD was assumed equal between rucaparib and niraparib in line with the assumption of comparable efficacy. Maximum treatment duration for rucaparib and niraparib was applied to the extrapolated TTD using exponential distribution.
Parametric function for PFS	Not applicable
Parametric function for OS	Log-normal
Inclusion of waste	Wastage was included based on the frequency of prescriptions (30 days), number of tablets required for the prescription period, number of packs required to provide tablets. The number of packs prescribed was calculated based on the distribution of actual doses for each month in the first 12 months of treatment, based on published data from the PRIMA study(37) and available in the ATHENA-MONO CSR(27). To avoid overestimating wastage on niraparib, a conservative approach was used by calculating the minimum wastage based on the sizes of packs dispensed. Wastage was then calculated based on discontinuation at the midpoint of the 30-day cycle, applied to patients who discontinued in each month, but not when ceasing treatment due to maximum treatment duration. Data on packs dispensed was not available in the ATHENA-MONO or PRIMA study or from other sources and therefore wastage among patients who experience dose interruptions and/or dose adjustments could not be calculated. It is assumed that at the individual patient-level, prescriptions will aim to minimise wastage.
Average time in model health state	On treatment - Rucaparib: [redacted] years - Niraparib: [redacted] years

12.1.1 Base case results

The results of the cost comparison are presented in Table 66.

Table 71 Base case results, discounted estimates

Costs, DKK	Rucaparib	Niraparib	Difference
Medicine costs,	[redacted]	[redacted]	[redacted]

Costs, DKK	Rucaparib	Niraparib	Difference
Medicine costs – co-administration	0	0	0
Administration	0	0	0
Disease management costs	[redacted]	[redacted]	[redacted]
Costs associated with management of adverse events	0	0	0
Subsequent treatment costs	[redacted]	[redacted]	[redacted]
Patient costs	[redacted]	[redacted]	[redacted]
Palliative care costs	0	0	0
Cost comparison	[redacted]	[redacted]	[redacted]

12.2 Sensitivity analyses

Uncertainty in the cost comparison was assessed through a deterministic sensitivity analyses based on scenarios.

12.2.1 Deterministic sensitivity analyses

In the cost comparison model, treatment duration and RDI represented a numeric input with associated uncertainty and was included in the one-way sensitivity. In addition, results using alternative assumptions on parameters used in the model were also included (Table 67). Due to the nature of this sensitivity analysis and lack of high/low values, a tornado diagram was not applicable.

Table 72 One-way sensitivity and scenario analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK) vs. niraparib
Base case			[redacted]

	Change	Reason / Rational / Source	Incremental cost (DKK) vs. niraparib
Excluding RDI	Exclude RDI in dose calculation	To test impact of excluding RDI	[redacted]
Excluding wastage	Exclude wastage assumption for all medicines	To test the impact of excluding wastage	[redacted]
Excluding patient time	Exclude costs related to patient time	To test the impact of removing patient time costs	[redacted]
TTD distribution: Weibull	Extrapolate TTD based on alternative distributional assumption	To test the impact of different distributional assumption for TTD	[redacted]
TTD distribution: Gompertz	Extrapolate TTD based on alternative distributional assumption	To test the impact of different distributional assumption for TTD	[redacted]
TTD distribution: Log-logistic	Extrapolate TTD based on alternative distributional assumption	To test the impact of different distributional assumption for TTD	[redacted]
TTD distribution: Log-normal	Extrapolate TTD based on alternative distributional assumption	To test the impact of different distributional assumption for TTD	[redacted]
TTD distribution: Gamma	Extrapolate TTD based on alternative distributional assumption	To test the impact of different distributional assumption for TTD	[redacted]
TTD distribution: Gen. Gamma	Extrapolate TTD based on alternative distributional assumption	To test the impact of different distributional assumption for TTD	[redacted]

12.2.2 Probabilistic sensitivity analyses

The cost comparison included only two uncertain parameters: length of treatment, and RDI. A probabilistic sensitivity analysis (PSA) was therefore performed to test the parametric uncertainty of these two numeric values. For duration of treatment, new parameters for the extrapolation were generated using the mean, standard error, and covariance matrix of the relevant coefficients; for RDI, a standard error of 10% of the mean value was used when the SE was not available. 5000 simulations were run, and a final average of the probabilistic cost comparison was calculated.

Compared to the base case cost comparison of [redacted] vs. niraparib, the probabilistic result was [redacted]. A convergence plot for the estimated mean cost comparison value is

presented in Figure 19. The histogram of incremental costs compared to niraparib are provided in Figure 20.

Figure 21 Convergence plot - cost comparison PSA

Figure 22 Histogram of incremental costs: rucaparib vs. niraparib

13. Budget impact analysis

Number of patients (including assumptions of market share)

Table 73 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		
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Non-recommendation		
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Budget impact

Table 74 Expected budget impact of recommending the medicine for the indication, [million] DKK

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

14. List of experts

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Appendix A. Main characteristics of studies included

The main characteristics of the studies included in the assessment are presented in the tables below.

Trial name: ATHENA-MONO	**NCT number: NCT03522246**
Objective	To evaluate the efficacy of rucaparib as maintenance therapy in a broad population (including those without mutations or other evidence of HRD, or high-risk clinical characteristics such as residual disease) with newly diagnosed ovarian cancer following response to front line platinum-based chemotherapy.
Publications – title, author, journal, year	• Monk BJ, Coleman RL, Fujiwara K, et al. ATHENA (GOG-3020/ENGOT-ov45): a randomized, phase III trial to evaluate rucaparib as monotherapy (ATHENA-MONO) and rucaparib in combination with nivolumab (ATHENA-COMBO) as maintenance treatment following frontline platinum-based chemotherapy in ovarian cancer. Int J Gynecol Cancer. 2021 Dec;31(12):1589-1594. • Kristeleit R, Ghamande S, Lim M, et al. 527MO Rucaparib maintenance treatment in patients (pts) with newly diagnosed ovarian cancer (OC): defining benefit according to disease risk subgroups within the phase 3 ATHENA-MONO study. Annals of oncology. 2022;33:S786-S787. doi:10.1016/j.annonc.2022.07.655. • Kristeleit R, O'Malley D, Lim MC, et al. Interim post-progression data and updated survival in patients with newly diagnosed advanced ovarian cancer in ATHENA-MONO. Gynecologic oncology. 2024/11/01/ 2024;190:S10-S11. • Kristeleit RS. Updated Progression-Free Survival In Patients With Newly Diagnosed Advanced Ovarian Cancer Treated With Rucaparib In ATHENA-MONO. 2024. • O'Malley D, Christopoulou A, Lim M, et al. Efficacy Analysis by Disease Risk Subgroup for the Phase 3 Athena-Mono Study (Gog- 3020/Engot-Ov45) Evaluating Rucaparib Maintenance Treatment in Patients with Newly Diagnosed Ovarian Cancer. International journal of gynecological cancer. 2022;32:2022-09. doi:10.1136/ijgc-2022-igcs.28 • O'Malley DM, Monk BJ, Lim MC, et al. Final safety results from ATHENA–MONO (GOG-3020/ENGOT-ov45), a randomized, placebo-controlled, double-blind, phase 3 trial evaluating rucaparib monotherapy as maintenance treatment in patients with newly diagnosed ovarian cancer. Journal of Clinical Oncology. 2024;42(16_suppl):5554-5554. • S. Ghamande, R. E. Miller, E. Solovyeva, et al. ATHENA-MONO Post-Progression Survival Data Update In Patients With Newly Diagnosed Advanced Ovarian Cancer . International Journal of Gynecological Cancer. 2025;35(2)
Study type and design	ATHENA-MONO is a randomised, international, double-blind, placebo-controlled, multicentre, phase III study that evaluated the efficacy and safety

Trial name: ATHENA-MONO		NCT number: NCT03522246
	of rucaparib monotherapy vs. placebo as maintenance therapy in patients with newly diagnosed advanced, high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer following a response to 1L platinum-based chemotherapy. Eligible patients were randomised in a 4:1 ratio to receive oral rucaparib (600 mg twice daily) + intravenous placebo (rucaparib group) or matching oral placebo + intravenous placebo (placebo group). Randomisation was computer generated (block size of 10) and was carried out within 8 weeks of day 1 of the last cycle of platinum-based chemotherapy. Patients were stratified by HRD classification, disease status after chemotherapy, and timing of surgery.	
Sample size (n)	538 (427 randomised to rucaparib and 111 randomised to placebo).	

Main inclusion criteria	• Have signed an IRB/IEC approved ICF prior to any study-specific evaluation.
	• 18 years or older (20 years or older in South Korea, Taiwan and Japan) at the time the ICF was signed.
	• Have newly diagnosed, histologically confirmed, advanced (FIGO Stage III-IV), high-grade ovarian, fallopian tube or primary peritoneal cancer.
	• Completed cytoreductive surgery either prior to chemotherapy (primary surgery) or following neoadjuvant chemotherapy (interval debulking).
	• Received 4-8 cycles of 1L platinum-doublet treatment, including a minimum of 4 cycles of platinum/taxane combination.
	  • A patient with best response of PR must have received at least 6 cycles.
	  • Bevacizumab was allowed during the chemotherapy phase, but not during maintenance.
	• Completed 1L platinum-based chemotherapy and surgery with a response, in the opinion of the investigator defined as no evidence of disease progression radiologically or through rising CA-125 at any time during front-line treatment; and
	  • No evidence of measurable disease by RECIST v1.1 (if complete resection at primary or interval cytoreductive surgery); or
	  • A partial or complete response per RECIST v1.1 (if measurable disease was present after surgery and prior to chemotherapy); or
	  • A CA-125 response (if only non-measurable disease was present after surgery and prior to chemotherapy).
	• Pre-treatment CA-125 measurements must have met criterion specified below:
	  • If the first value was within ULN the patient was eligible to be randomised and a second sample was not required.	

Trial name: ATHENA-MONO	NCT number: NCT03522246
	• If the first value was greater than ULN a second assessment must have been performed at least 7 days after the first; if the second assessment was ≥15% than the first value the patient was not eligible. • Patient must have been randomised within 8 weeks of the first day of the last cycle of chemotherapy. • Had sufficient FFPE tumour tissue (1 × 4 µm section for haematoxylin & eosin stain and approximately 8 to 12 × 10 µm sections, or equivalent) available for planned analyses. • Adequate bone marrow, hepatic and renal function. • ECOG PS of 0 to 1.
Main exclusion criteria	• Non-epithelial tumours or ovarian tumours with low malignant potential or mucinous tumours. • Mixed mullerian tumours/carcinosarcomas were allowed. • Active second malignancy. • Patients with a history of malignancy that had been completely treated, with no evidence of active cancer for 3 years prior to enrolment, or patients with surgically cured low-risk tumours, such as early-stage cervical or endometrial cancer were allowed to enrol. • Known central nervous system brain metastases. • Any prior treatment for ovarian cancer, other than the 1L platinum regimen, including any maintenance treatment between completion of the platinum regimen and initiation of study drug in this study. • Ongoing hormonal treatment for previously treated breast cancer was permitted. • Hormonal maintenance treatment for ovarian cancer was not allowed. • Had evidence of interstitial lung disease, active pneumonitis, myocarditis, or a history of myocarditis. • Patients with an active, known or suspected autoimmune disease. • Patients with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger were permitted to enrol. • Patients with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, were permitted in the absence of active autoimmune disease. • Drainage of ascites during the final 2 cycles of treatment with the platinum regimen.

Trial name: ATHENA-MONO	NCT number: NCT03522246

- Pre-existing duodenal stent and/or any gastrointestinal disorder defect that would have, in the opinion of the investigator, interfered with absorption of study treatment.
- Known history of a positive test for human immunodeficiency virus or known acquired immunodeficiency syndrome.
- Any positive test result for hepatitis B and/or known history of hepatitis B infection including patients with undetectable hepatitis B DNA and inactive carriers; positive test result for hepatitis C antibody.
- Pregnant, or breastfeeding.
    - All study participants must have avoided pregnancy achieved through assisted reproductive technology for the duration of study treatment and for a minimum of 6 months following the last dose of study drug (oral or IV, whichever was later).
- Received chemotherapy within 14 days prior to first dose of study drug and/or ongoing adverse effects from such treatment >NCI-CTCAE v5.0) Grade 1, with the exception of Grade 2 non-hematologic toxicity such as alopecia, peripheral neuropathy, Grade 2 anaemia with haemoglobin ≥9 g/Dl, and related effects of prior chemotherapy that were unlikely to be exacerbated by treatment with study drug.
- Non-study related minor surgical procedure ≤5 days, or major surgical procedure ≤21 days, prior to first dose of study drug; in all cases, the patient must have been sufficiently recovered and stable before treatment administration.
- Presence of any other condition that may have increased the risk associated with study participation or may have interfered with the interpretation of study results, and, in the opinion of the investigator, would have made the patient inappropriate for entry into the study.
- Hospitalisation for bowel obstruction within 12 weeks prior to enrolment.

Intervention	Rucaparib 600 mg was administered orally two times a day (as close as possible to 12 hours apart, preferably at the same times every day) with at least 240 ml of water starting on Day 1. Intravenous placebo was administered via a 30-minute intravenous infusion (100 ml total volume per infusion) on Day 1 of every 28 day cycle, starting on Cycle 2. 427 patients were randomised to the intervention arm.
Comparator(s)	Placebo was administered orally two times a day (as close as possible to 12 hours apart, preferably at the same times every day) with at least 240 ml of water starting on Day 1. Intravenous placebo was administered via a 30-minute intravenous infusion (100 ml total volume per infusion) on Day 1 of every 28 day cycle, starting on Cycle 2. 111 patients were randomised to the placebo arm.

Trial name: ATHENA-MONO	NCT number: NCT03522246
Follow-up time	The pre-specified DCO for ATHENA-MONO was 23 March 2022, with a median follow-up of 26 months.(7) An additional year of follow-up was presented to the EMA for OS, CFI, TFST, TSST and TTD with a DCO of 9 March 2023.(42, 92) Updated invPFS data was also published with a DCO of 1 March 2024.(51) The most recent ad-hoc analysis for invPFS and PFS2 is dated 17 May 2024 (approximately 4 years follow-up).(39, 43, 44)
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	Endpoints included in this application: The primary endpoint was invPFS. OS was a secondary endpoint while FACT-O, EQ-5D-5L, PFS2 and TTD were exploratory endpoints. Other endpoints: Other secondary endpoints were BICR-assessed PFS, ORR and DOR. CFI, TFST and TSST were included as exploratory endpoints in the study, but results are not included in this application.
Method of analysis	All efficacy analyses were intention-to-treat analyses. Outcomes relevant for the submission (invPFS, PFS2, OS and TTD) were also assessed in the non-tBRCA, HRD+ cohort (pre-specified) and non-tBRCA, HRD– cohort (post-hoc). Stratified log-rank test was used for treatment comparisons. Hazard ratios were estimated with stratified Cox proportional hazard models.
Subgroup analyses	Pre-planned subgroup analyses were performed based on randomisation stratification subgroups, HRD and gene mutation information, and baseline demographic characteristics: • HRD population • HRD test status (BRCA mutation, LOH high/low/unknown) • Disease status after chemotherapy (no residual disease, residual disease) • Timing of surgery (primary surgery, interval debulking) • Age (<65, 65–74, ≥75, <75 years) • Race (White, non-white, unknown) • ECOG PS (0, ≥1) • FIGO status at diagnosis (III, IV) • Disease burden at baseline (no disease, non-target disease, measurable disease) • CA-125 at baseline (normal, above normal) • Previous use of bevacizumab (yes, no)

Trial name: ATHENA-MONO	NCT number: NCT03522246
	• Best response to chemotherapy (no disease after surgery, CR, PR, not evaluable/other) • Disease-free with normal CA-125 (yes, no) • Cytoreductive surgery outcome (complete resection, other outcome) The non-tBRCA, HRD+ cohort was pre-specified. Data for the non-tBRCA, HRD– cohort were generated post-hoc by combining data from patients from two pre-specified subgroups (non-tBRCA, LOH low and non-tBRCA, LOH unknown). Patient characteristics of the non-tBRCA, HRD+ and non-tBRCA, HRD– cohorts are presented in the main body of the submission.
Other relevant information	N/A

1L = first-line; BICR = blinded independent central review; BRCA = breast cancer gene; CA-125 = cancer antigen 125; CFI = chemotherapy-free interval; DCO = data cut-off; DNA = deoxyribonucleic acid; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EMA = European Medicines Agency; EQ-5D-5L = EuroQol 5 Dimension 5 Level; FACT-O = Functional Assessment of Cancer Therapy – Ovarian; FFPE = formalin-fixed, paraffin-embedded; FIGO = International Federation of Gynecology and Obstetrics; HRD = homologous recombination deficiency; ICF = informed consent form; invPFS = investigator-assessed progression-free survival; IRB/IEC = institutional review board/independent ethics committee; LOH = loss of heterozygosity; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PFS = progression-free survival; PFS2 = progression-free survival to second progression; PR = partial response; ORR = overall response rate; OS = overall survival; RECIST = response evaluation criteria in solid tumuors; TSFT = time to first subsequent therapy; TSST = time to second subsequent therapy; TTD = time to treatment discontinuation.

Table 75 Main characteristic of studies included – PRIMA(54)

Trial name: PRIMA	NCT number: NCT02655016
Objective	To test the efficacy and safety of niraparib maintenance therapy after a response to platinum-based chemotherapy in patients with newly diagnosed advanced ovarian cancer at high risk for relapse.
Publications – title, author, journal, year	Mirza MR, Gonzalez Martin A, Graybill W, et al. Evaluation of an individualized starting-dose of niraparib in the PRIMA/ENGOT-OV26/GOG-3012 study. American Society of Clinical Oncology; 2020. Chase DM, Marín MR, Backes F, et al. Impact of disease progression on health-related quality of life of advanced ovarian cancer patients – Pooled analysis from the PRIMA trial. Gynecologic oncology. 2022/09/01/ 2022;166(3):494-502. Monk BJ, Barretina-Ginesta MP, Pothuri B, et al. Niraparib first-line maintenance therapy in patients with newly diagnosed advanced ovarian cancer: final overall survival results from the PRIMA/ENGOT-OV26/GOG-3012 trial. Annals of oncology : official journal of the European Society for Medical Oncology. Nov 2024;35(11):981-992.

Trial name: PRIMA	NCT number: NCT02655016
	González-Martín A, Pothuri B, Vergote I, et al. Progression-free survival and safety at 3.5 years of follow-up: results from the randomised phase 3 PRIMA/ENGOT-OV26/GOG-3012 trial of niraparib maintenance treatment in patients with newly diagnosed ovarian cancer. European Journal of Cancer. 2023;189 González-Martín A, Pothuri B, Vergote I, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. New England Journal of Medicine. 2019;381(25):2391-2402.
Study type and design	PRIMA is a randomized, double blinded, placebo controlled, phase III study of niraparib versus placebo. Eligible patients were randomised 2:1 to receive niraparib or placebo. Randomisation was performed in a double-blind manner with the use of an interactive Web-response system, with stratification according to clinical response after first-line platinum-based chemotherapy (complete or partial response), receipt of neoadjuvant chemotherapy (yes or no), and status regarding tumour homologous recombination (deficient vs. proficient or not determined)
Sample size (n)	733 (487 randomised to niraparib and 246 randomised to placebo)
Main inclusion criteria	• At least 18 years of age. • Newly diagnosed, histologically confirmed advanced cancer of the ovary, peritoneum, or fallopian tube (collectively defined as ovarian cancer). • High-grade serous or endometrioid tumours that were classified as stage III or IV, according to the criteria of the FIGO. Included in this category were patients with stage III disease with visible residual tumour after primary debulking surgery, inoperable stage III disease, or any stage IV disease, as well as those who had received neoadjuvant chemotherapy. • Receipt of six to nine cycles of first-line platinum-based chemotherapy before enrolment, which had resulted in a complete or partial response, according to investigator assessment. • Randomised within 12 weeks of the first day of the last cycle of chemotherapy. • Agree to undergo central tumour HRD testing.
Main exclusion criteria	• Mucinous or clear cell subtypes of epithelial ovarian cancer, carcinosarcoma or undifferentiated ovarian cancer. • Stage III disease and complete cytoreduction (i.e., no visible residual disease) after primary debulking surgery. • >2 debulking surgeries for the study disease. • Receipt of bevacizumab as maintenance treatment. Patients who have received bevacizumab with their first-line platinum based therapy but are unable to receive bevacizumab as maintenance therapy due to adverse events or any other reason are not excluded from study as long as the last

Trial name: PRIMA	NCT number: NCT02655016
	dose of bevacizumab was received ≥ 28 days prior to signing the main informed consent form. • Condition (such as transfusion dependent anaemia or thrombocytopenia), or laboratory abnormality that might confound the study results or interfere with the patient's participation for the full duration of the study treatment. • Pregnant, breastfeeding, or expecting to conceive children while receiving study treatment and for up to 180 days after the last dose of study treatment. • Known hypersensitivity to the components of niraparib or its excipients. • Investigational therapy administered within 4 weeks, or within a time interval less than at least 5 half-lives of the investigational agent, whichever is longer, prior to the first scheduled day of dosing in this study. • Any known ≥Grade 3 anaemia, neutropenia or thrombocytopenia due to prior chemotherapy that persisted >4 weeks. • Diagnosis and/or treatment for any invasive cancer (other than study disease) <5 years prior to study enrolment. Patients with definitively treated uterine cervical or urinary tract carcinoma in situ, non-melanomatous skin cancer or ductal carcinoma in situ (DCIS) of the breast are not excluded.
Intervention	Oral niraparib 300 mg (or 200 mg if weight <77 kg and/or platelet count <150,000 cm3) once daily in 28-day cycles for up to 36 months. The trial was amended on November 27, 2017, to incorporate an individualized starting dose of 200 mg once daily for some patients. 487 patients were randomised to the niraparib arm.
Comparator(s)	Matching placebo administered orally once daily in 28-day cycles for up to 36 months. 246 patients were randomised to the placebo arm.
Follow-up time	The pre-specified DCO for PRIMA was 17 May 2019, with a median follow-up of 13.8 months.(54) Additional PFS data were reported at the 17 December 2021 DCO (median follow-up 3.5 years).(89) The final OS analysis had a DCO of 8 April 2024 (median follow-up 73.9 months).(5)
Is the study used in the health economic model?	Yes.
Primary, secondary and exploratory endpoints	Endpoints included in this application: invPFS, OS and PFS2 were secondary endpoints. Other endpoints:

Trial name: PRIMA	NCT number: NCT02655016
	The primary endpoint (BICR-assessed PFS) was not included in this application. Other secondary endpoints were TFST, pharmacokinetic analyses, FACT-O, E5-5D-5L and EORTC-QLQ-C30/OV28, but results were not included in this application.
Method of analysis	All efficacy analyses were intention-to-treat analyses. Outcomes relevant for the submission (invPFS, PFS2 and OS) were also assessed in the non-tBRCA, HRD+ cohort (pre-specified). Hazard ratios and 95% CI for subgroups relevant to the submission were calculated using unstratified Cox proportional hazards model.
Subgroup analyses	Pre-planned subgroup analyses were performed based on: • Dose (fixed starting dose, individualised starting dose) • Age (<65 years, ≥65 years) • Region (North America, Rest of the World) • ECOG PS (0, 1) • FIGO stage (III, IV) • Receipt of neoadjuvant chemotherapy (yes, no) • Response to 1L platinum-based chemotherapy (CR, PR) • HRD status (BRCA mutation, HRD high/low/unknown) The non-tBRCA, HRD+ and non-tBRCA, HRD– cohorts were pre-specified. Patient characteristics of these cohorts are presented in the main body of the submission.
Other relevant information	N/A

1L = first-line; BICR = blinded independent central review; BRCA = breast cancer gene; CI = confidence interval; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; DCO = data cut-off; EORTC-QLQ-C30/OV28 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30/Ovarian Cancer Module; EQ-5D-5L = EuroQol 5 Dimension 5 Level; FACT-O = Functional Assessment of Cancer Therapy – Ovarian; FIGO = International Federation of Gynecology and Obstetrics; HRD = homologous recombination deficiency; invPFS = investigator-assessed progression-free survival; PFS = progression-free survival; PR = partial response; PFS2 = progression-free survival to second progression; OS = overall survival; TSFT = time to first subsequent therapy; tBRCA = tumour tissue mutation in breast cancer gene; ULN = upper limit of normal

Table 76 Main characteristic of studies included – PAOLA-1(10)

Trial name: PAOLA-1	NCT number: NCT02477644
Objective	To evaluate maintenance therapy with olaparib as compared with placebo in patients with newly diagnosed advanced ovarian cancer who were receiving chemotherapy plus bevacizumab followed by bevacizumab, regardless of BRCA mutation status.

Trial name: PAOLA-1	NCT number: NCT02477644
Publications – title, author, journal, year	Gonzalez Martin AJ, Medioni J, Harter P, et al. 36MO Maintenance olaparib plus bevacizumab (bev) in patients (pts) with newly diagnosed advanced ovarian cancer (OC): 5-year (y) progression-free survival (PFS) by molecular subgroup in the PAOLA-1/ENGOT-ov25 trial. ESMO Open. 2023;8(1) Harter P, Mouret-Reynier MA, Pignata S, et al. Efficacy of maintenance olaparib plus bevacizumab according to clinical risk in patients with newly diagnosed, advanced ovarian cancer in the phase III PAOLA-1/ENGOT-ov25 trial. Gynecologic oncology. 2022/02/01/ 2022;164(2):254-264. González-Martín A, Desauw C, Heitz F, et al. Maintenance olaparib plus bevacizumab in patients with newly diagnosed advanced high-grade ovarian cancer: Main analysis of second progression-free survival in the phase III PAOLA-1/ENGOT-ov25 trial. Eur J Cancer. Oct 2022;174:221-231. Ray-Coquard I, Leary A, Pignata S, et al. Olaparib plus bevacizumab first-line maintenance in ovarian cancer: final overall survival results from the PAOLA-1/ENGOT-ov25 trial. Annals of Oncology. 2023;34(8):681-692. Kurtz JE, Anota A, Cropet C, et al. Quality of life in patients with advanced high-grade ovarian cancer (HGOC) receiving maintenance therapies after first-line (1L) chemotherapy in the randomized phase III PAOLA-1/ENGOT-ov25 trial (NCT02477644). Journal of Clinical Oncology. 2022;40(16_suppl):5560-5560. Hietanen S, Pautier P, Harter P, et al. RECIST/CA-125 progression-free survival and the role of CA-125 surveillance in the phase III PAOLA-1/ENGOT-ov25 trial evaluating maintenance olaparib plus bevacizumab in patients with newly diagnosed advanced high-grade ovarian carcinoma. Gynecologic oncology. 2021/08/01/ 2021;162:S71. Lorusso D, Mouret-Reynier MA, Harter P, et al. Updated progression-free survival and final overall survival with maintenance olaparib plus bevacizumab according to clinical risk in patients with newly diagnosed advanced ovarian cancer in the phase III PAOLA-1/ENGOT-ov25 trial. Int J Gynecol Cancer. Apr 1 2024;34(4):550-558. Ray-Coquard I, Pautier P, Pignata S, et al. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. The New England journal of medicine. Dec 19 2019;381(25):2416-2428.
Study type and design	Randomized, double blinded, phase III study of olaparib plus bevacizumab vs. placebo plus bevacizumab. Patients were randomly assigned in a 2:1 ratio to receive olaparib or placebo. Randomization was performed centrally with the use of a block design with stratification according to the outcome of first-line treatment at screening and tumour BRCA status. Patients were assigned to olaparib tablets or matching placebo tablets with the use of an interactive Web or voice response system.
Sample size (n)	806 (537 randomised to olaparib plus bevacizumab and 269 randomised to placebo plus bevacizumab).

Trial name: PAOLA-1	NCT number: NCT02477644

Main inclusion criteria	• At least 18 years of age.
	• Signed informed consent and ability to comply with treatment and follow-up.
	• Newly diagnosed ovarian cancer, primary peritoneal cancer and/or fallopian tube cancer
	  • Histologically confirmed (based on local histopathological findings) high-grade serous, high-grade endometrioid or other epithelial non-mucinous ovarian cancer in patients with a deleterious germline BRCA1 and/or BRCA2 mutation
	  • Advanced stage (FIGO 1998 stage IIIB, IIIC or IV or FIGO 2014 stage IIIA–IV)
	• Completed first-line, platinum-taxane chemotherapy prior to randomization.
	• Prior to randomization, patients must have received a minimum of three cycles of bevacizumab in combination with the three last cycles of platinum-based chemotherapy. Only in the case of interval cytoreductive surgery are patients permitted to receive only two cycles of bevacizumab in combination with the last three cycles of platinum-based chemotherapy. Bevacizumab treatment should be administered at a dose 15 mg/kg every 3 weeks up to a total of 15 months.
	• Prior to randomization, patients must be without evidence of disease or in complete response or partial response from the first-line treatment.
	• Patients must be randomized at least 3 weeks and no more than 9 weeks after their last dose of chemotherapy (last dose is the day of the last infusion) and all major toxicities from prior chemotherapy must have resolved to NCI-CTCAE grade 1 or better (except alopecia and peripheral neuropathy.
	• Patients must have normal organ and bone marrow function.
	• ECOG PS of 0 to 1.
	• Formalin-fixed, paraffin-embedded tumour sample from the primary cancer must be available for central BRCA testing and test result must be available for stratification.
	• Postmenopausal or evidence of non-childbearing status for women of childbearing potential prior to the first dose of study treatment.
	• For France only: in France, a patient will be eligible for randomization in this study only if either affiliated to, or a beneficiary of, a social security category.

Main exclusion criteria	• Non-epithelial origin of the ovary, the fallopian tube or the peritoneum. • Ovarian tumours of low malignant potential (e.g., borderline tumours) or mucinous carcinoma. • Synchronous primary endometrial cancer unless Stage II AND the patient was aged <60 years at the time of diagnosis of endometrial cancer with

Trial name: PAOLA-1	NCT number: NCT02477644
	stage IA or IB grade I or II, or stage IA grade III endometrial carcinoma OR aged ≥60 years at the time of diagnosis of endometrial cancer with stage IA grade I or II endometrioid adenocarcinoma. • Serous or clear cell adenocarcinoma or carcinosarcoma of the endometrium. • Other malignancy within the last 5 years except adequately treated non-melanoma skin cancer; curatively treated in situ cancer of the cervix; ductal carcinoma in situ. Patients with a history of localized malignancy diagnosed over 5 years ago may be eligible provided they completed adjuvant systemic therapy prior to randomization and remain free of recurrent or metastatic disease. Patients with a history of primary triple-negative breast cancer may be eligible provided they completed definitive anticancer treatment more than 3 years ago and remain breast cancer free prior to start of study treatment. • Patients with myelodysplastic syndromes/acute myeloid leukaemia history.
Intervention	Oral olaparib 300 mg twice daily at least 3 and no more than 9 weeks after the last dose of chemotherapy for up to 24 months. Intravenous bevacizumab, initiated with chemotherapy and continued as maintenance therapy, at a dose of 15 mg/kg of body weight every 3 weeks for a total duration of 15 months. 537 patients were randomised to the olaparib plus bevacizumab arm.
Comparator(s)	Matching placebo administered orally twice daily at least 3 and no more than 9 weeks after the last dose of chemotherapy for up to 24 months. Intravenous bevacizumab, initiated with chemotherapy and continued as maintenance therapy, at a dose of 15 mg/kg of body weight every 3 weeks for a total duration of 15 months. 269 patients were randomised to the placebo plus bevacizumab arm.
Follow-up time	The pre-specified DCO for PAOLA-1 was 22 March 2019, with a median follow-up of 22.9 months.(10) The final OS analysis had a DCO 22 March 2022 (median follow-up 62 months).(6)
Is the study used in the health economic model?	Yes.
Primary, secondary and exploratory endpoints	Endpoints included in this application: The primary endpoint was invPFS. OS and PFS2 were secondary endpoints. Other endpoints: EORTC-QLQ-C30 was also assessed as a secondary endpoint, but results were not included in this application.

Trial name: PAOLA-1	NCT number: NCT02477644
Method of analysis	All efficacy analyses were intention-to-treat analyses. Outcomes relevant for the submission (invPFS, PFS2 and OS) were also assessed in the non-tBRCA, HRD– cohort (pre-specified). The Kaplan–Meier method was used to estimate progression-free survival, with the stratified log-rank test used to assess the difference between the olaparib group and the placebo group. The hazard ratio and associated 95% CI were calculated with the use of a stratified Cox proportional-hazards model.
Subgroup analyses	Pre-planned subgroup analyses were performed based on: • Age (<65 years, ≥65 years) • FIGO stage (III, IV) • ECOG PS (0, 1) • 1L treatment outcome at screening (no evidence of disease, PR) • Cytoreductive surgery outcome (no residual disease, residual disease) • Timing of cytoreductive surgery (upfront, interval, no surgery) • Response to 1L chemotherapy (no evidence of disease, CR, PR) • CA-125 at baseline (normal, above normal) • Tumour BRCA mutation status (mutation, no mutation or unknown) • HRD status (positive, negative, negative or unknown, unknown)
Other relevant information	N/A

1L = first-line; BRCA = breast cancer gene; CA-125 = cancer antigen 125; CI = confidence interval; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; DCO = data cut-off; FIGO = International Federation of Gynecology and Obstetrics; HRD = homologous recombination deficiency; invPFS = investigator-assessed progression-free survival; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PR = partial response; PFS2 = progression-free survival to second progression; OS = overall survival; tBRCA = tumour tissue mutation in breast cancer gene

Appendix B. Efficacy results per study

Results per study

Results per study for all trials included in this assessment are presented in the tables below.

B.1 ATHENA-MONO (NCT03522246)

Table 77 Results per study (ATHENA-MONO [NCT03522246]) – non-tBRCA, HRD+ population

Results of ATHENA-MONO (NCT03522246) in the non-tBRCA, HRD+ population											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value		
Median invPFS (23 March 2022 DCO)	Rucaparib	94	20.3 (13.4, 31.1) months	NR	NR	NR	HR: 0.58	0.30, 1.00	0.058	Non-parametric survival analysis (Kaplan-Meier, unstratified HR calculation [including log-rank test]) and parametric survival analysis.	Monk et al. 2022(7)
	Placebo	25	9.2 (4.0, 22.1) months								
Median invPFS (5 May 2025 DCO)	Rucaparib	94	22.3 (13.4, 31.1) months	NR	NR	NR	HR: 0.58	0.35, 0.96		Non-parametric survival analysis (Kaplan-Meier, unstratified HR calculation [including log-rank test]) and parametric survival analysis.	Kristeleit et al.(53)
	Placebo	25	9.2 (4.0, 21.7) months								

Results of ATHENA-MONO (NCT03522246) in the non-tBRCA, HRD+ population											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value		
Median BIRC-assessed PFS (23 March 2022 DCO)	Rucaparib	94	27.8 (16.8, NR) months							The stratified log-rank test was considered the primary analysis. A stratified Cox proportional hazard model was used to calculate HR between treatment groups.	Monk et al. 2022(7)
	Placebo	25	9.1 (3.6, 17.5) months	NR	NR	NR	HR: 0.46	0.26, 0.81	0.0072		
Median OS (23 March 2022 DCO)	Rucaparib	94	Not reached	NR	NR	NR	HR: 0.64	0.25, 1.59	0.3331	Non-parametric survival analysis (Kaplan-Meier, unstratified HR calculation [including log-rank test]) and parametric survival analysis.	Monk et al. 2022(7)
	Placebo	25	Not reached								
Median OS (9 March 2023 DCO)	Rucaparib	94	Not reached	NR	NR	NR	[redacted]	[redacted]	[redacted]	Non-parametric survival analysis (Kaplan-Meier, unstratified HR calculation [including log-rank test]) and parametric survival analysis.	Pharma& data on file(92)
	Placebo	25	[redacted]								
Median PFS2 (14	Rucaparib	94	[redacted]	NR	NR	NR	[redacted]	[redacted]	[redacted]	Non-parametric survival analysis (Kaplan-Meier,	

Results of ATHENA-MONO (NCT03522246) in the non-tBRCA, HRD+ population											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value		
May 2024 DCO)	Placebo	25	[redacted]							unstratified HR calculation [including log-rank test]) and parametric survival analysis.	Pharma& data on file(43)
Median PFS2 (5 May 2025 DCO)	Rucaparib	94	37.4 months	NR	NR	NR	HR: 0.91	0.50, 1.67		Non-parametric survival analysis (Kaplan-Meier, unstratified HR calculation [including log-rank test]) and parametric survival analysis.	Kristeleit et al.(53)
	Placebo	25	31.2 months								
Median CFI (9 March 2023 DCO)	Rucaparib	94	28.0 (NR) months	NR	NR	NR	HR: 0.54	0.32, 0.93	0.0253	The stratified log-rank test was considered the primary analysis. A stratified Cox proportional hazard model was used to calculate HR between treatment groups.	Rucaparib EMA assessment report(42)
	Placebo	25	13.5 (NR) months								
Median TFST (9 March 2023 DCO)	Rucaparib	94	26.1 (NR) months	NR	NR	NR	HR: 0.55	0.33, 0.95	0.0303	The stratified log-rank test was considered the primary analysis. A stratified Cox proportional hazard model was used to calculate HR between treatment groups.	Rucaparib EMA assessment report(42)
	Placebo	25	12.0 (NR) months								

Results of ATHENA-MONO (NCT03522246) in the non-tBRCA, HRD+ population											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value		
Median TFST (5 May 2025 DCO)	Rucaparib	94	26.6 (NR) months	NR	NR	NR	HR: 0.63	0.37, 1.06		The stratified log-rank test was considered the primary analysis. A stratified Cox proportional hazard model was used to calculate HR between treatment groups.	Kristeleit et al.(53)
	Placebo	25	12.0 (NR) months								
Median TSST (9 March 2023 DCO)	Rucaparib	94	36.9 (NR) months	NR	NR	NR	HR: 0.70	0.37, 1.33	0.2796	The stratified log-rank test was considered the primary analysis. A stratified Cox proportional hazard model was used to calculate HR between treatment groups.	Rucaparib EMA assessment report(42)
	Placebo	25	29.0 (NR) months								
Median TTD (9 March 2023 DCO)	Rucaparib	94	[redacted]	NR	NR	NR	[redacted]	[redacted]	[redacted]	Non-parametric survival analysis (Kaplan-Meier, unstratified HR calculation [including log-rank test]) and parametric survival analysis.	Pharma& data on file(92)
	Placebo	25	[redacted]								

BICR = blinded independent central review; CI = confidence interval; CFI = chemotherapy-free interval; DCO = data cut-off; HR = hazard ratio; HRD = homologous recombination deficiency; invPFS = investigator-assessed progression-free survival; NR = not reported; OS = overall survival; PFS = progression-free survival; PFS2 = progression-free survival to second progression; TSFT = time to first subsequent therapy; TSST = time to second subsequent therapy; TTD = time to treatment discontinuation; tBRCA = tumour tissue mutation in breast cancer gene

Table 78 Results per study (ATHENA-MONO [NCT03522246]) –HRD+ population

Results of ATHENA-MONO (NCT03522246) in the HRD+ population (used in the MAIC)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value		
Median invPFS (17 May 2024 DCO)	Rucaparib	185	[redacted]	NR	NR	NR	[redacted]	[redacted]	[redacted]	Non-parametric survival analysis (Kaplan-Meier, unstratified HR calculation [including log-rank test]) and parametric survival analysis.	Pharma& data on file(43)
	Placebo	49	[redacted]								
Median OS (9 March 2023 DCO)	Rucaparib	185	NR (NR, NR) months	NR	NR	NR	HR: 0.84	0.44, 1.58	0.581	Non-parametric survival analysis (Kaplan-Meier, unstratified HR calculation [including log-rank test]) and parametric survival analysis.	Kristeleit et al.(42, 53)
	Placebo	49	NR (41.0-NR) months								
Median PFS2 (17 May 2024 DCO)	Rucaparib	185	57.3 months	NR	NR	NR	[redacted]	[redacted]	[redacted]	Non-parametric survival analysis (Kaplan-Meier, unstratified HR calculation [including log-rank test]) and parametric survival analysis.	Pharma& data on file(43)
	Placebo	49	39.9 months								

BICR = blinded independent central review; CI = confidence interval; CFI = chemotherapy-free interval; DCO = data cut-off; HR = hazard ratio; HRD = homologous recombination deficiency; invPFS = investigator-assessed progression-free survival; NR = not reported; OS = overall survival; PFS = progression-free survival; PFS2 = progression-free survival to second progression; TSFT = time to first subsequent therapy; TSST = time to second subsequent therapy; TTD = time to treatment discontinuation; tBRCA = tumour tissue mutation in breast cancer gene

Table 79 Results per study (PRIMA [NCT02655016]) – non-tBRCA, HRD+ population

Results of PRIMA (NCT02655016) - non-tBRCA, HRD+ population											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value		
Median invPFS (17 May 2019 DCO)	Niraparib	95	19.6 (13.6, not estimable)	NR	NR	NR	HR: 0.50	0.31, 0.83	0.006	HR and 95% CI were calculated using stratified Cox proportional hazards model.	González-Martín et al. 2019(54)
	Placebo	55	8.2 (6.7, 16.8)								
Median invPFS (17 November 2021 DCO)	Niraparib	95	NR (NR)	NR	NR	NR	HR: 0.66	0.44, 1.00	NR	HR and 95% CI were calculated using stratified Cox proportional hazards model.	González-Martín et al. 2023(89)
	Placebo	55	NR (NR)								
Median invPFS (8 April 2024 DCO)	Niraparib	94	19.4 (NR)	NR	NR	NR	HR: 0.67	0.45, 1.00	NR	HR and 95% CI were calculated using stratified Cox proportional hazards model.	Monk et al. 2024(5)
	Placebo	55	10.4 (NR)								
Median OS (8 April 2024 DCO)	Niraparib	94	NR (NR)	NR	NR	NR	HR: 0.97	0.62, 1.53	NR	HR and 95% CI were calculated using unstratified Cox proportional hazards model.	Monk et al. 2024(5)
	Placebo	55	NR (NR)								
	Niraparib	94	38.0 (NR)	NR	NR	NR	HR: 0.88	0.57, 1.36	NR		

Results of PRIMA (NCT02655016) - non-tBRCA, HRD+ population											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value		
Median PFS2 (8 April 2024 DCO)	Placebo	55	34.1 (NR)							HR and 95% CI were calculated using unstratified Cox proportional hazards model.	Monk et al. 2024(5)
Median TFST (9 April 2024 DCO)	Niraparib	94	22.5 (NR)	NR	NR	NR	HR: 0.76	0.50-1.14	NR	HR and 95% CI were calculated using unstratified Cox proportional hazards model.	Monk et al. 2024(5)
	Placebo	55	12.9 (NR)								

CI = confidence interval; DCO = data cut-off; HR = hazard ratio; HRD = homologous recombination deficiency; invPFS = investigator-assessed progression-free survival; NR = not reported; OS = overall survival; PFS2 = progression-free survival to second progression; TSFT = time to first subsequent therapy; tBRCA = tumour tissue mutation in breast cancer gene

Table 80 Results per study (PRIMA [NCT02655016]) – HRD+ population

Results of PRIMA (NCT02655016) - HRD+ population (used in the MAIC)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value		
Median invPFS (8 April 2024 DCO)	Niraparib	247	24.5 (NR)	NR	NR	NR	HR: 0.51	0.40, 0.66	NR	HR and 95% CI were calculated using stratified Cox proportional hazards model.	Monk et al. 2024(5)
	Placebo	126	11.2 (NR)								
Median OS (8 April 2024 DCO)	Niraparib	247	71.9 (NR)	NR	NR	NR	HR: 0.95	0.70, 1.29	NR	HR and 95% CI were calculated using unstratified Cox proportional hazards model.	Monk et al. 2024(5)
	Placebo	126	69.8 (NR)								
Median PFS2 (8 April 2024 DCO)	Niraparib	247	43.4 (NR)	NR	NR	NR	HR: 0.87	0.66, 1.17	NR	HR and 95% CI were calculated using unstratified Cox proportional hazards model.	Monk et al. 2024(5)
	Placebo	126	39.3 (NR)								

CI = confidence interval; DCO = data cut-off; HR = hazard ratio; HRD = homologous recombination deficiency; invPFS = investigator-assessed progression-free survival; NR = not reported; OS = overall survival; PFS2 = progression-free survival to second progression; TSFT = time to first subsequent therapy; tBRCA = tumour tissue mutation in breast cancer gene

Table 81 Results per study (PAOLA-1 [NCT02477644]) – non-tBRCA HRD+ population

Results of PAOLA-1 (NCT02477644) - non-tBRCA HRD+ population											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value		
Median invPFS (22 March 2022 DCO)	Olaparib plus bevacizumab	97	30.0 (21.9, 60.3) months	NR	NR	NR	HR: 0.47	0.32, 0.70	NR	PFS was estimated using the KM method and compared between arms by stratified log-rank tests. HRs and CIs were estimated from stratified Cox proportional hazards models.	González-Martín et al. 2023(71)
	Placebo plus bevacizumab	55	16.6 (12.9, 19.5) months								
Median OS (22 March 2022 DCO)	Olaparib plus bevacizumab	97	NR (NR) months	NR	NR	NR	HR: 0.71	0.45, 1.13	NR	OS was estimated using the KM method and compared between arms by stratified log-rank tests. HRs and CIs were estimated from stratified Cox proportional hazards models.	Ray-Coquard et al. 2023(6)
	Placebo plus bevacizumab	55	52.0 (NR) months								
Median PFS2 (22	Olaparib plus bevacizumab	97	50.3 (NR) months	NR	NR	NR	HR: 0.60	0.38, 0.96	NR	HR and 95% CI were calculated using stratified Cox proportional hazards model.	González-Martín et al. 2022(70)

Results of PAOLA-1 (NCT02477644) - non-tBRCA HRD+ population											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value		
March 2020 DCO)	Placebo plus bevacizumab	55	30.1 (NR) months								

CI = confidence interval; DCO = data cut-off; HR = hazard ratio; HRD = homologous recombination deficiency; invPFS = investigator-assessed progression-free survival; KM = Kaplan–Meier; NR = not reported; OS = overall survival; PFS2 = progression-free survival to second progression; tBRCA = tumour tissue mutation in breast cancer gene

Table 82 Results per study (PAOLA-1 [NCT02477644]) – HRD+ population

Results of PAOLA-1 (NCT02477644) - HRD+ population (used in the MAIC)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value		
Median invPFS (22 March 2022 DCO)	Olaparib plus bevacizumab	255	46.8 (36.4, 65.7) months	NR	NR	NR	HR: 0.41	0.32, 0.54	NR	PFS was estimated using the KM method and compared between arms by stratified log-rank tests. HRs and CIs were estimated from stratified Cox proportional hazards models.	Ray-Coquard et al. 2023(6)
	Placebo plus bevacizumab	132	17.6 (15.8, 20.3) months								

Results of PAOLA-1 (NCT02477644) - HRD+ population (used in the MAIC)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value		
Median OS (22 March 2022 DCO)	Olaparib plus bevacizumab	255	75.2 (NR) months	NR	NR	NR	HR: 0.62	0.45, 0.85	NR	OS was estimated using the KM method and compared between arms by stratified log-rank tests. HRs and CIs were estimated from stratified Cox proportional hazards models.	Ray-Coquard et al. 2023(6)
	Placebo plus bevacizumab	132	57.3 (NR) months								
Median PFS2 (22 March 2020 DCO)	Olaparib plus bevacizumab	255	50.3 (NR) months	NR	NR	NR	HR: 0.56	0.41, 0.77	NR	HR and 95% CI were calculated using stratified Cox proportional hazards model.	Ray-Coquard et al. 2023(6)
	Placebo plus bevacizumab	132	35.5 (NR) months								

CI = confidence interval; DCO = data cut-off; HR = hazard ratio; HRD = homologous recombination deficiency; invPFS = investigator-assessed progression-free survival; KM = Kaplan–Meier; NR = not reported; OS = overall survival; PFS2 = progression-free survival to second progression; tBRCA = tumour tissue mutation in breast cancer gene

Appendix C. Comparative analysis of efficacy

The methods for the MAIC are described in detail in Section 7.1.2 for the comparison of rucaparib to niraparib and Section 7.2.2 for the comparison of rucaparib to olaparib plus bevacizumab.

C.1 MAIC results

Table 83 Comparative analysis of studies comparing rucaparib to niraparib for patients with ovarian cancer in HRD+ population(91)

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**		
invPFS	ATHENA-MONO (rucaparib) and PRIMA (niraparib)	NA	NA	NA	[redacted]	[redacted]	[redacted]	The HRs for the studies included were synthesized using an anchored MAIC.	N/A
PFS2	ATHENA-MONO (rucaparib) and PRIMA (niraparib)	NA	NA	NA	[redacted]	[redacted]	[redacted]	The HRs for the studies included were synthesized using an anchored MAIC.	N/A
OS	ATHENA-MONO (rucaparib) and PRIMA (niraparib)	NA	NA	NA	[redacted]	[redacted]	[redacted]	The HRs for the studies included were synthesized using an anchored MAIC.	N/A

CI = confidence interval; HR = hazard ratio; HRD = homologous recombination deficiency; invPFS = investigator-assessed progression-free survival; MAIC = matching-adjusted indirect comparison; NA = not available; OS = overall survival; PFS2 = progression-free survival to second progression

Table 84 Comparative analysis of studies comparing rucaparib to olaparib in combination with bevacizumab for patients with ovarian cancer in the HRD+ population(91)

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**		
invPFS	ATHENA-MONO (rucaparib) and PAOLA-1 (olaparib plus bevacizumab)	NA	NA	NA	[redacted]	[redacted]	[redacted]	The HRs for the studies included were synthesized using an unanchored MAIC.	N/A
PFS2	ATHENA-MONO (rucaparib) and PAOLA-1 (olaparib plus bevacizumab)	NA	NA	NA	[redacted]	[redacted]	[redacted]	The HRs for the studies included were synthesized using an unanchored MAIC.	N/A
OS	ATHENA-MONO (rucaparib) and PAOLA-1 (olaparib plus bevacizumab)	NA	NA	NA	[redacted]	[redacted]	[redacted]	The HRs for the studies included were synthesized using an unanchored MAIC.	N/A

CI = confidence interval; HR = hazard ratio; HRD = homologous recombination deficiency; invPFS = investigator-assessed progression-free survival; MAIC = matching-adjusted indirect comparison; NA = not available; OS = overall survival; PFS2 = progression-free survival to second progression

C.2 Distribution of weights

C.2.1 ATHENA-MONO vs. PRIMA (niraparib)

Figure 23 ATHENA-MONO vs. PRIMA MAIC - Distribution of weights in the placebo arm

Figure 24 ATHENA-MONO vs. PRIMA MAIC - Distribution of weights in the rucaparib arm

C.2.2 ATHENA-MONO vs. PAOLA-1 (olaparib plus bevacizumab)

Figure 25 ATHENA-MONO vs. PAOLA-1 MAIC - Distribution of weights in the rucaparib arm

C.3 Testing the PH assumptions

C.3.1 ATHENA-MONO vs. PAOLA-1 (olaparib plus bevacizumab)

Table 85. PH assumption diagnostics of invPFS for rucaparib in ATHENA-MONO vs. olaparib + bevacizumab in PAOLA-1

Log-cumulative hazards plot

Schoenfeld residuals plot

Time-varying Cox model					
Model Type	Variable	Hazard-ratio	Lower 95%CI	Upper 95%CI	p-value
Natural time	Treatment	[redacted]	[redacted]	[redacted]	[redacted]
	Treatment * time	[redacted]	[redacted]	[redacted]	[redacted]
Log-time	Treatment	[redacted]	[redacted]	[redacted]	[redacted]
	Treatment * log(time)	[redacted]	[redacted]	[redacted]	[redacted]

Notation: Index study arm = ATHENA-MONO, rucaparib (DCO: 17/05/2024); Comparator study arm = PAOLA-1, olaparib + bevacizumab (Ray-Coquard et al., 2019; DCO: 22 March 2019)

Table 86. PH assumption diagnostics of PFS2 for rucaparib in ATHENA-MONO vs. olaparib + bevacizumab in PAOLA-1

Log-cumulative hazards plot

Schoenfeld residuals plot

Time-varying Cox model					
Model Type	Variable	Hazard-ratio	Lower 95%CI	Upper 95%CI	p-value
Natural time	Treatment	[redacted]	[redacted]	[redacted]	[redacted]
	Treatment * time	[redacted]	[redacted]	[redacted]	[redacted]
Log-time	Treatment	[redacted]	[redacted]	[redacted]	[redacted]
	Treatment * log(time)	[redacted]	[redacted]	[redacted]	[redacted]

Notation: Index study arm = ATHENA-MONO, rucaparib (DCO: 17/05/2024); Comparator study arm = PAOLA-1, olaparib + bevacizumab (González-Martín et al., 2022; DCO 22 March 2020)

Table 87. PH assumption diagnostics of OS for rucaparib in ATHENA-MONO vs. olaparib + bevacizumab in PAOLA-1

Log-cumulative hazards plot

Schoenfeld residuals plot

Time-varying Cox model					
Model Type	Variable	Hazard-ratio	Lower 95%CI	Upper 95%CI	p-value
Natural time	Treatment	[redacted]	[redacted]	[redacted]	[redacted]
	Treatment * time	[redacted]	[redacted]	[redacted]	[redacted]
Log-time	Treatment	[redacted]	[redacted]	[redacted]	[redacted]
	Treatment * log(time)	[redacted]	[redacted]	[redacted]	[redacted]

Notation: Index study arm = ATHENA-MONO, rucaparib (DCO: 09/03/2023); Comparator study arm = PAOLA-1, olaparib + bevacizumab (Ray-Coquard et al., 2023; DCO: 22 March 2022)

C.3.2 ATHENA-MONO vs. PRIMA (niraparib)

Table 88. PH assumption diagnostics of invPFS for rucaparib and placebo in ATHENA-MONO after adjustment against PRIMA

Log-cumulative hazards plot

Schoenfeld residuals plot

Time-varying Cox model					
Model Type	Variable	Hazard-ratio	Lower 95%CI	Upper 95%CI	p-value
Natural time	Treatment	[redacted]	[redacted]	[redacted]	[redacted]
	Treatment * time	[redacted]	[redacted]	[redacted]	[redacted]
Log-time	Treatment	[redacted]	[redacted]	[redacted]	[redacted]
	Treatment * log(time)	[redacted]	[redacted]	[redacted]	[redacted]

Notation: Index study, active arm = ATHENA-MONO, rucaparib (DCO: 17/05/2024); Index study, anchor arm = ATHENA-MONO, placebo (DCO: 17/05/2024)

Table 89. PH assumption diagnostics of invPFS for rucaparib in ATHENA-MONO after adjustment vs. niraparib in PRIMA

Log-cumulative hazards plot

Schoenfeld residuals plot

Time-varying Cox model					
Model Type	Variable	Hazard-ratio	Lower 95%CI	Upper 95%CI	p-value
Natural time	Treatment	[redacted]	[redacted]	[redacted]	[redacted]
	Treatment * time	[redacted]	[redacted]	[redacted]	[redacted]
Log-time	Treatment	[redacted]	[redacted]	[redacted]	[redacted]
	Treatment * log(time)	[redacted]	[redacted]	[redacted]	[redacted]

Notation: Index study, active arm = ATHENA-MONO, rucaparib (DCO: 17/05/2024); Index study, anchor arm = ATHENA-MONO, placebo (DCO: 17/05/2024); Comparator study, active arm = PRIMA, niraparib (DCO: 08 April 2024); Comparator study, anchor arm = PRIMA, placebo (DCO: 08 April 2024)

Table 90. PH assumption diagnostics of OS for rucaparib and placebo in ATHENA-MONO after adjustment against PRIMA

Log-cumulative hazards plot

Schoenfeld residuals plot

Time-varying Cox model					
Model Type	Variable	Hazard-ratio	Lower 95%CI	Upper 95%CI	p-value
Natural time	Treatment	[redacted]	[redacted]	[redacted]	[redacted]
	Treatment * time	[redacted]	[redacted]	[redacted]	[redacted]
Log-time	Treatment	[redacted]	[redacted]	[redacted]	[redacted]
	Treatment * log(time)	[redacted]	[redacted]	[redacted]	[redacted]

Notation: Index study, active arm = ATHENA-MONO, rucaparib (DCO: 09/03/2023); Index study, anchor arm = ATHENA-MONO, placebo (DCO: 09/03/2023)

Table 91. PH assumption diagnostics of OS for rucaparib in ATHENA-MONO after adjustment vs. niraparib in PRIMA

Log-cumulative hazards plot

Schoenfeld residuals plot

Time-varying Cox model					
Model Type	Variable	Hazard-ratio	Lower 95%CI	Upper 95%CI	p-value
Natural time	Treatment	[redacted]	[redacted]	[redacted]	[redacted]
	Treatment * time	[redacted]	[redacted]	[redacted]	[redacted]
Log-time	Treatment	[redacted]	[redacted]	[redacted]	[redacted]
	Treatment * log(time)	[redacted]	[redacted]	[redacted]	[redacted]

Notation: Index study, active arm = ATHENA-MONO, rucaparib (DCO: 09/03/2023); Index study, anchor arm = ATHENA-MONO, placebo (DCO: 09/03/2023); Comparator study, active arm = PRIMA, niraparib (Monk BJ et al., 2024); Comparator study, anchor arm = PRIMA, placebo (Monk BJ et al., 2024)

C.4 Piecewise unanchored MAIC – rucaparib vs. olaparib plus bevacizumab for invPFS and PFS2

C.4.1 Summary of Piecewise Unanchored MAIC Results

Table 92. Unanchored MAIC for invPFS assuming piecewise constant HR over two time periods (t=15 months)

Comparator Treatment	MAIC Adjustment	Time period 1: [0, t), HR (95% CI)	Time period 2: [t, ∞), HR (95% CI)
Olaparib + bevacizumab (PAOLA-1)	Unadjusted (N=185)	[redacted]	[redacted]
	Adjusted (ESS=[redacted])	[redacted]	[redacted]

Abbreviation: CI, confidence interval; HR, hazard ratio; ESS, estimated sample size; invPFS, investigator-assessed progression-free survival; MAIC, matching adjusted indirect comparison

Table 93. Unanchored MAIC for PFS2 assuming piecewise constant HR over two time periods (t=15 months)

Comparator Treatment	MAIC Adjustment	Time period 1: [0, t), HR (95% CI)	Time period 2: [t, ∞), HR (95% CI)
Olaparib + bevacizumab (PAOLA-1)	Unadjusted (N=185)	[redacted]	[redacted]
	Adjusted (ESS=[redacted])	[redacted]	[redacted]

Abbreviation: CI, confidence interval; HR, hazard ratio; ESS, estimated sample size; MAIC, matching adjusted indirect comparison; PFS2, progression-free survival to second progression

C.4.2 Diagnostics for Piecewise Unanchored MAIC

Figure 26. Unanchored MAIC for invPFS assuming piecewise constant HR over two time periods (t=15 months) in HRD+ population

Figure 27. Unanchored MAIC for PFS2 assuming piecewise constant HR over two time periods (t=15 months) in HRD+ population

Appendix D. Extrapolation

Not applicable

D.1 Extrapolation of time to treatment discontinuation (TTD)

D.1.1 Data input

Data informing time to treatment discontinuation is collected in the ATHENA-MONO trial.

TTD data were taken from the ATHENA-MONO trial's DCO of 09 March 2023, however the timeframe was truncated at [redacted] weeks for non-tBRCA HRD+ population to reflect the 2-year stopping rule. Median TTD for the rucaparib arm in the HRD+ population [redacted] weeks and [redacted] weeks for placebo. There were [redacted] events (approximately [redacted] maturity) with more events in the placebo arm ([redacted] vs. [redacted]). The sample sizes were [redacted] in the rucaparib arm and [redacted] in the placebo arm. There was a maximum follow-up of [redacted] weeks.

KM curves for TTD for the oral rucaparib and oral placebo treatment arms in the HRD+population are presented in Figure 28.

Figure 28 KM Plot of TTD in ATHENA-MONO non-tBRCA HRD+ Population

Abbreviations: HRD = homologous recombination deficiency; KM = Kaplan–Meier; TTD = time to treatment discontinuation

D.1.2 Model

Standard parametric distributions were fitted to the patient-level data for the rucaparib arm of the trial to provide long-term extrapolations. Full detail of the methodology and selection process for the models is reported in Section 8.1.

D.1.3 Proportional hazards

Statistical tests were conducted to test if the proportional hazards (PH) and accelerated failure time (AFT) assumptions hold between the two treatment arms of ATHENA-MONO within the observed trial follow-up period. A full description of the methods to test for PH and AFT assumptions is reported Section 8.1.

PH assessment based on time dependent Cox regression model did not find a significant interaction between the treatment effect and time (or log-time), and the Schoenfeld residual test was non-significant (p-value=0.32). The log-cumulative hazard curves for rucaparib and placebo crossed (Figure 29), which indicated a potential violation of the PH assumption. The QQ plot showed a non-linear pattern of quantiles of observed survival times, suggesting a violation of the AFT (Figure 30).

Due to potential violation of the AFT assumption, and better visual fit when overlaying fitted curves to trial KM curves, separate parametric fits for rucaparib and placebo trial arms were considered to be appropriate. Given that routine surveillance is not a comparator in the non-tBRCA HRD+ population, only the extrapolated curves for rucaparib were reported in this section.

Figure 29 Log-cumulative hazard plot of TTD for rucaparib and placebo in ATHENA-MONO

Abbreviation: TTD = time to treatment discontinuation

Figure 30 QQ plots for TTD for rucaparib and placebo in ATHENA-MONO

Abbreviation: TTD = time to treatment discontinuation

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

Table 94 below summarises the AIC and BIC that measure the fit to the data while taking into account the complexity of the parametric models. Lower values indicate better fit. The lowest values for each are indicated in bold print.

Table 94 Statistical Fit of TTD Parametric Curves Within ATHENA-MONO—non-tBRCA HRD+

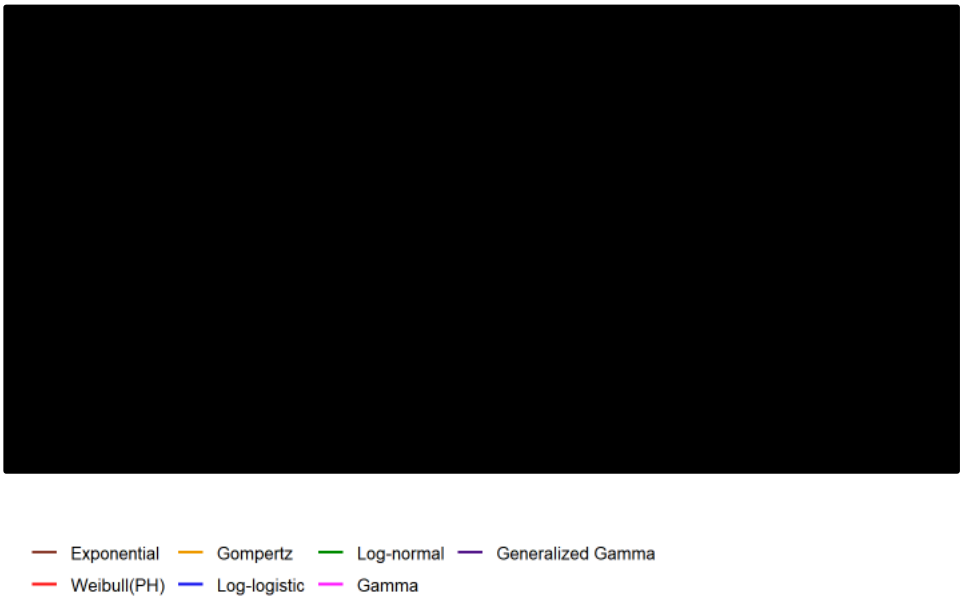
	Oral Rucaparib	
	AIC	**BIC**
Exponential	674.1	676.7
Weibull(PH)	675.9	681
Gompertz	676.1	681.2
Log-logistic	674.5	679.6
Log-normal	676	681.1
Gamma	675.8	680.9
Generalised Gamma	676.7	684.4

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; HRD = homologous recombination deficiency; TTD = time to treatment discontinuation; PH = proportional hazards

D.1.5 Evaluation of visual fit

Predicted curves from models fitted to each group separately (independent fits) are shown in Figure 31. Agreement between the observed and predicted curves suggests adequate fit to the observed data.

Figure 31 Parametric Curve Fits to Rucaparib and Placebo TTD KM Data for the non-tBRCA HRD+ Population



Abbreviations: HRD = homologous recombination deficiency; KM = Kaplan–Meier; TTD = time to treatment discontinuation

D.1.6 Evaluation of hazard functions

Due to potential violation of PH and AFT assumptions, and better visual fit when overlaying fitted curves to trial KM curves, separate parametric fits for rucaparib and placebo trial arms were considered to be appropriate.

Based on the assessment of smoothed hazards in Figure 32, the hazard function for rucaparib remained roughly constant over time. This suggests that the exponential distribution could be an appropriate choice to inform the extrapolation.

Figure 32 Smoothed hazards plot for TTD in the non-tBRCA HRD+ population of ATHENA-MONO

D.1.7 Validation and discussion of extrapolated curves

Assessment of the visual and statistical fit of the OS curves was deemed acceptable to determine the distribution for TTD given the maturity of the patient-level data from ATHENA and reasonably similar extrapolations across distributions. Exponential distribution has lowest AIC/BIC and adequate visual fit.

D.1.8 Adjustment of background mortality

No further adjustment for background mortality was applied in the model, due to the following:

- Death is considered an event in the time-to-discontinuation model, therefore extrapolated values already include overall survival
- Deaths observed in the model considerably exceed background mortality rates in the general population within the included time horizon.

D.1.9 Adjustment for treatment switching/cross-over

Not applicable since there was no treatment cross-over in the ATHENA-MONO Study.

D.1.10 Waning effect

Not applicable since there is no biological or clinical rationale for assuming a waning effect.

D.1.11 Cure-point

Not applicable.

D.2 Extrapolation of overall survival (OS)

D.2.1 Data input

Data informing overall free survival is collected in the ATHENA-MONO trial (see Section 6.2.1).

Median OS was [redacted] in the rucaparib arm in the non-tBRCA HRD+ population of the ATHENA-MONO trial at the DCO of 09 March 2023. Median OS for the placebo arm in was [redacted]. There were [redacted] events (approximately [redacted] maturity) with more events in the placebo arm ([redacted] vs. [redacted]). The sample sizes were [redacted] in the rucaparib arm and [redacted] in the placebo arm. There was a maximum follow-up of [redacted] weeks.

KM curves for OS for the oral rucaparib and oral placebo treatment arms in the HRD+ population are presented in Figure 33.

Figure 33 KM Plot of OS in ATHENA-MONO non-tBRCA HRD+ Population

[redacted]

Abbreviations: HRD = homologous recombination deficiency; KM = Kaplan–Meier; OS = overall survival

D.2.2 Model

Standard parametric distributions were fitted to the patient-level data for the rucaparib arm of the trial to provide long-term extrapolations.

D.2.3 Proportional hazards

Statistical tests were conducted to test if the proportional hazards (PH) and accelerated failure time (AFT) assumptions hold between the two treatment arms of ATHENA-MONO within the observed trial follow-up period.

PH assessment based on time dependent Cox regression model did not find a significant interaction between the treatment effect and time (or log-time), and the Schoenfeld residual test was non-significant (p-value=0.606). The log-cumulative hazard curves for rucaparib and placebo crossed (Figure 34), which indicated a potential violation of the PH assumption. The QQ plot showed a non-linear pattern of quantiles of observed survival times, suggesting a potential violation of the AFT (Figure 35).

Due to potential violation of the PH and AFT assumptions, and better visual fit when overlaying fitted curves to trial KM curves, separate parametric fits for rucaparib and placebo trial arms were considered to be appropriate. Given that routine surveillance is not a comparator in the non-tBRCA HRD+ population, only the extrapolated curves for rucaparib were reported in this section.

Figure 34 Log-cumulative hazard plot of OS for rucaparib and placebo in ATHENA-MONO

Abbreviation: OS = Overall survival

Figure 35 QQ plots for OS for rucaparib and placebo in ATHENA-MONO

Abbreviation: OS = Overall survival

D.2.4 Evaluation of statistical fit for standard parametric models (AIC and BIC)

Table 95 below summarises the AIC and BIC that measure the fit to the data while taking into account the complexity of the parametric models. Lower values indicate better fit. The lowest values for each are indicated in bold print.

Table 95 Statistical Fit of OS Parametric Curves Within ATHENA-MONO, non-tBRCA HRD+

	Oral Rucaparib	
	AIC	**BIC**
Exponential	400.2	402.7
Weibull(PH)	396.4	401.4
Gompertz	399.4	404.5
Log-logistic	395.5	400.6
Log-normal	394.2	399.3
Gamma	395.7	400.8

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; HRD = homologous recombination deficiency; OS = Overall survival; PH = proportional hazards

D.2.5 Evaluation of visual fit

Predicted curves from models fitted to each group separately (independent fits) are shown in Figure 36. Agreement between the observed and predicted curves suggests adequate fit to the observed data.

Figure 36 Parametric Curve Fits to Rucaparib and Placebo OS KM Data for the non-tBRCA HRD+ Population

Exponential Gompertz Log-normal Generalized Gamma
Weibull(PH) Log-logistic Gamma

Abbreviations: HRD = homologous recombination deficiency; KM = Kaplan–Meier; OS = overall survival

D.2.6 Evaluation of hazard functions

Based on the assessment of smoothed hazards in Figure 37, the hazard function for rucaparib is non-monotonic and gradually reduces over time after reaching a peak around 84 weeks. This suggests that a distribution which captures a flattening in the survival curve (e.g., log-normal), or a flexible spline model could be an appropriate choice to inform the extrapolation.

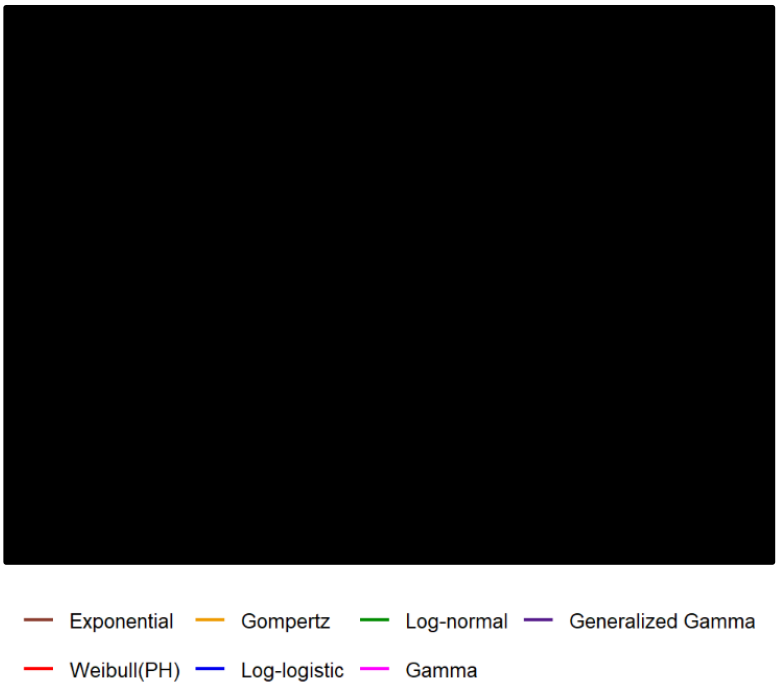
Figure 37 Smoothed hazards plot for OS in the non-tBRCA HRD+ population of ATHENA-MONO

Abbreviations: HRD = homologous recombination deficiency; KM = Kaplan–Meier; OS = overall survival

D.2.7 Evaluation of standard parametric models

The log-normal distribution had the lowest AIC and BIC for rucaparib. Based on visual inspection, the log-normal distribution provided the best fit to the KM data and adequately captured the tail of the OS curve.

Figure 38 Projected OS for rucaparib in the non-tBRCA HRD+ population of ATHENA-MONO



Abbreviations: HRD = homologous recombination deficiency; KM = Kaplan–Meier; OS = overall survival

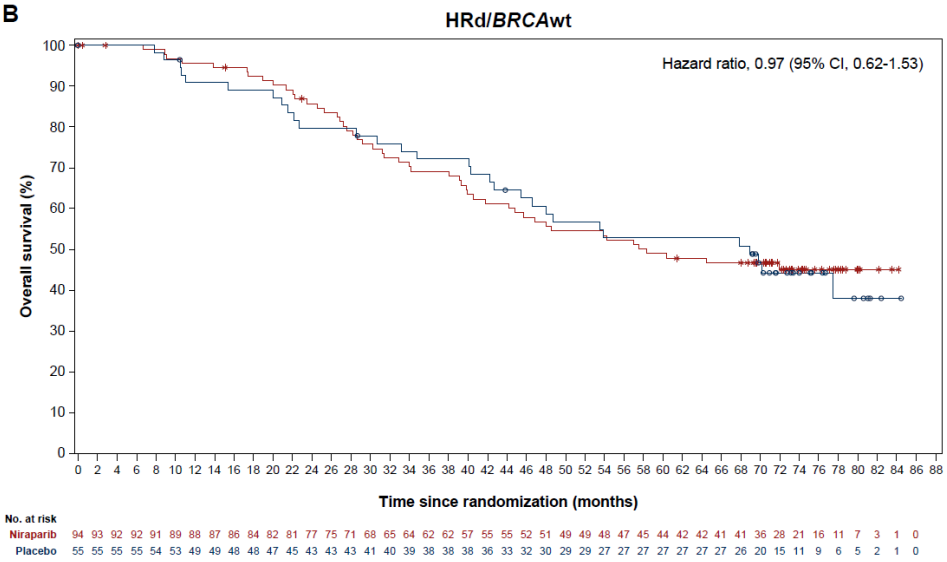
D.2.8 Validation and discussion of extrapolated curves

The log-normal standard parametric model had the lowest AIC/BIC and provides a plausible extrapolation.

The clinical plausibility of the extrapolated OS in the model was validated using long-term follow-up data from the HRD/BRCAwt subgroup of the PRIMA trial (Figure 39).(5)

The extrapolation approach used in the model base case was validated by a clinical expert in Denmark. The expert agreed with the overall approach for extrapolation of overall survival, and that the extrapolated survival was in alignment with their experience in clinical practice.

Figure 39 Long-term OS in the HRd/BRCAwt subgroup of PRIMA trial



D.2.9 Adjustment of background mortality

As the mortality in this population considerably exceeds background mortality rates in the general population for the time horizon considered in the model, no adjustments were performed.

D.2.10 Adjustment for treatment switching/cross-over

Not applicable since there was no treatment cross-over in the ATHENA-MONO Study.

D.2.11 Survival curve capping rules

Not applicable.

D.2.12 Waning effect

Not applicable since there is no biological or clinical rationale for assuming a waning effect.

D.2.13 Cure-point

The presence of long-term survivorship in advanced ovarian cancer is supported by analyses of long-term data from mature chemotherapy trials(96). Furthermore, the presence of a proportion of patients who achieve sustained remission that can be equal to cure was confirmed by a clinical expert advising the NICE committee for the technology appraisal of rucaparib in 1L aOC (Dr. Agnieszka Michael).(94) Although a cure fraction was not explicitly modelled, the effect of a cure on long-term survival was captured using parametric models which account for a reduction in the rate of progression and death over time.

D.3 Extrapolation of [effect measure 2]

[For each effect measure please, fill in this section using the same template as stated in section D.1]

Appendix E. Serious adverse events

The serious adverse events reported for each study included in this application are presented in the tables below. The full list of serious AEs in ATHENA-MONO, PRIMA, and PAOLA-1 are presented in Table 89, , and Table 91, respectively(27, 85, 97).

Table 96 ATHENA-MONO SAEs (23 March 2022 DCO)(27)

ITT population	Rucaparib (n=425)	Placebo (n=110)
Overall	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Acute coronary syndrome	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Angioedema	[redacted]	[redacted]
Appendicitis	[redacted]	[redacted]
Ascites	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Atypical pneumonia	[redacted]	[redacted]
Brucellosis	[redacted]	[redacted]
Cerebrovascular accident	[redacted]	[redacted]
Cholecystitis acute	[redacted]	[redacted]
Clear cell renal cell carcinoma	[redacted]	[redacted]
Clostridium difficile infection	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]
Deep vein thrombosis	[redacted]	[redacted]

ITT population	Rucaparib (n=425)	Placebo (n=110)
Dehydration	[redacted]	[redacted]
Diaphragmatic hernia	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Enteritis	[redacted]	[redacted]
Enterocolitis infectious	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Gastrointestinal stoma complication	[redacted]	[redacted]
Haematoma	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]
Ileus	[redacted]	[redacted]
Incisional hernia	[redacted]	[redacted]
Infected lymphocele	[redacted]	[redacted]
Influenza	[redacted]	[redacted]
Infusion related reaction	[redacted]	[redacted]
Intervertebral disc protrusion	[redacted]	[redacted]
Intestinal obstruction	[redacted]	[redacted]
Malignant neoplasm progression	[redacted]	[redacted]
Multiple injuries	[redacted]	[redacted]
Multiple organ dysfunction syndrome	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]

ITT population	Rucaparib (n=425)	Placebo (n=110)
Nodular melanoma	[redacted]	[redacted]
Pancreatic neuroendocrine tumour	[redacted]	[redacted]
Pancytopenia	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Product administration error	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]
Pyelonephritis	[redacted]	[redacted]
Pyelonephritis acute	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Rectal haemorrhage	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Small intestinal obstruction	[redacted]	[redacted]
Syncope	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Tibia fracture	[redacted]	[redacted]
Transaminases increased	[redacted]	[redacted]
Tubulointerstitial nephritis	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Urosepsis	[redacted]	[redacted]
Urticaria	[redacted]	[redacted]
Vaginal infection	[redacted]	[redacted]
Vascular access complication	[redacted]	[redacted]

ITT population	Rucaparib (n=425)	Placebo (n=110)
Viral infection	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]

Table 97 PRIMA SAEs (Primary analysis (up to month 34)(85)

ITT population	Niraparib (n=484)	Placebo (n=244)
All-cause mortality	48 (9.9%)	31 (12.7%)
Anaemia	27 (5.6%)	0 (0.0%)
Febrile neutropenia	3 (0.6%)	0 (0.0%)
Neutropenia	6 (1.2%)	0 (0.0%)
Pancytopenia	1 (0.2%)	0 (0.0%)
Thrombocytopenia	59 (12.2%)	0 (0.0%)
Sinus tachycardia	1 (0.2%)	1 (0.4%)
Ventricular tachycardia	0 (0.0%)	1 (0.4%)
Retinal detachment	1 (0.2%)	0 (0.0%)
Abdominal fat apron	0 (0.0%)	1 (0.4%)
Abdominal pain	1 (0.2%)	2 (0.8%)
Abdominal pain lower	1 (0.2%)	0 (0.0%)
Abdominal pain upper	0 (0.0%)	1 (0.4%)
Diarrhoea	1 (0.2%)	0 (0.0%)
Enteritis	1 (0.2%)	0 (0.0%)
Ileus	0 (0.0%)	1 (0.4%)
Intestinal obstruction	5 (1.0%)	1 (0.4%)
Intestinal perforation	1 (0.2%)	0 (0.0%)
Large intestinal obstruction	1 (0.2%)	0 (0.0%)
Nausea	0 (0.0%)	1 (0.4%)

ITT population	Niraparib (n=484)	Placebo (n=244)
Small intestinal obstruction	14 (2.9%)	5 (2.0%)
Subileus	0 (0.0%)	2 (0.8%)
Vomiting	1 (0.2%)	1 (0.4%)
Fatigue	1 (0.2%)	0 (0.0%)
Gait disturbance	1 (0.2%)	0 (0.0%)
General physical health deterioration	1 (0.2%)	0 (0.0%)
Pyrexia	0 (0.0%)	1 (0.4%)
Cholecystitis	1 (0.2%)	0 (0.0%)
Abdominal abscess	0 (0.0%)	1 (0.4%)
Appendicitis	1 (0.2%)	0 (0.0%)
Cellulitis	1 (0.2%)	1 (0.4%)
Enterocolitis infectious	1 (0.2%)	0 (0.0%)
Infected lymphocele	1 (0.2%)	1 (0.4%)
Infection	0 (0.0%)	1 (0.4%)
Influenza	1 (0.2%)	1 (0.4%)
Lung infection	2 (0.4%)	0 (0.0%)
Neutropenic sepsis	1 (0.2%)	0 (0.0%)
Pneumonia	3 (0.6%)	0 (0.0%)
Pneumonia fungal	1 (0.2%)	0 (0.0%)
Pyelonephritis	1 (0.2%)	0 (0.0%)
Skin bacterial infection	1 (0.2%)	0 (0.0%)
Urinary tract infection	1 (0.2%)	2 (0.8%)
Femoral neck fracture	1 (0.2%)	0 (0.0%)
Hip fracture	0 (0.0%)	2 (0.8%)
Intentional overdose	0 (0.0%)	1 (0.4%)

ITT population	Niraparib (n=484)	Placebo (n=244)
Overdose	8 (1.6%)	3 (1.2%)
Postoperative hernia	1 (0.2%)	0 (0.0%)
Transfusion reaction	1 (0.2%)	0 (0.0%)
Wound complication	1 (0.2%)	0 (0.0%)
Hepatic enzyme increased	1 (0.2%)	0 (0.0%)
International normalised ratio increased	1 (0.2%)	0 (0.0%)
Neutrophil count decreased	1 (0.2%)	0 (0.0%)
Platelet count decreased	20 (4.1%)	0 (0.0%)
Decreased appetite	1 (0.2%)	0 (0.0%)
Arthralgia	1 (0.2%)	0 (0.0%)
nvasive ductal breast carcinoma	1 (0.2%)	1 (0.4%)
Metastases to breast	0 (0.0%)	1 (0.4%)
Metastases to central nervous system	2 (0.4%)	1 (0.4%)
Myelodysplastic syndrome	1 (0.2%)	0 (0.0%)
Papillary thyroid cancer	0 (0.0%)	1 (0.4%)
Squamous cell carcinoma	0 (0.0%)	1 (0.4%)
Thyroid cancer	1 (0.2%)	0 (0.0%)
Aphasia	1 (0.2%)	1 (0.4%)
Device occlusion	1 (0.2%)	0 (0.0%)
Anxiety	1 (0.2%)	0 (0.0%)
Confusional state	1 (0.2%)	0 (0.0%)
Depression	1 (0.2%)	0 (0.0%)
Insomnia	1 (0.2%)	0 (0.0%)
Mania	1 (0.2%)	0 (0.0%)
Mental status changes	1 (0.2%)	0 (0.0%)

ITT population	Niraparib (n=484)	Placebo (n=244)
Psychotic disorder	1 (0.2%)	0 (0.0%)
Ureteric stenosis	1 (0.2%)	0 (0.0%)
Urethral stenosis	1 (0.2%)	0 (0.0%)
Urinary retention	1 (0.2%)	0 (0.0%)
Dyspnoea	0 (0.0%)	2 (0.8%)
Pleural effusion	1 (0.2%)	0 (0.0%)
Pneumonitis	4 (0.8%)	0 (0.0%)
Pulmonary embolism	1 (0.2%)	0 (0.0%)
Fasting	0 (0.0%)	1 (0.4%)
Hypertension	1 (0.2%)	0 (0.0%)
Lymphocele	2 (0.4%)	1 (0.4%)

Table 98 PAOLA-1 SAEs (22 March 2019 DCO)(10)

Adverse event, n (%)	Olaparib plus bevacizumab (N=535)	Placebo plus bevacizumab (N=267)
Any	167 (31)	83 (31)
Hypertension	48 (9)	35 (13)
Anemia*	34 (6)	1 (<1)
Intestinal obstruction†	16 (3)	5 (2)
Embolism‡	8 (1)	1 (<1)
Neutropenia§	5 (1)	1 (<1)
Abdominal pain¶	4 (1)	2 (1)
Thrombocytopenia**	4 (1)	1 (<1)
Ileus	3 (1)	3 (1)
Coronary artery disease††	3 (1)	1 (<1)
Erysipelas	3 (1)	1 (<1)
Pyrexia	3 (1)	1 (<1)
Depression	3 (1)	0
General physical health deterioration	3 (1)	0
Myelodysplastic syndrome	3 (1)	0
Diarrhea	2 (<1)	2 (1)
Dyspnea‡‡	2 (<1)	1 (<1)
Infection	2 (<1)	1 (<1)
Cardiac failure§§	2 (<1)	0
CMV infection	2 (<1)	0
Fistula¶¶	2 (<1)	0
Hypotension	2 (<1)	0
Interstitial lung disease	2 (<1)	0
Lymphocele	2 (<1)	0
Pneumonia	2 (<1)	0
Pneumonitis	2 (<1)	0
URTI***	2 (<1)	0
Vomiting	2 (<1)	0
Intestinal perforation†††	1 (<1)	2 (1)
Anxiety	1 (<1)	1 (<1)
Breast cancer	1 (<1)	1 (<1)
Device-related infection	1 (<1)	1 (<1)
Hydronephrosis	1 (<1)	1 (<1)
Infected lymphocele	1 (<1)	1 (<1)
Proteinuria	1 (<1)	1 (<1)
Spinal fracture	1 (<1)	1 (<1)
Abdominal abscess	1 (<1)	0
Abdominal wall abscess	1 (<1)	0
Acute myeloid leukemia	1 (<1)	0
Allergic edema	1 (<1)	0
Aplastic anemia	1 (<1)	0
Back pain	1 (<1)	0
Bacteremia	1 (<1)	0

Adverse event, n (%)	Olaparib plus bevacizumab (N=535)	Placebo plus bevacizumab (N=267)
Beta hemolytic streptococcal infection	1 (<1)	0
Device-associated breast complication	1 (<1)	0
Bronchial carcinoma	1 (<1)	0
Cementoplasty	1 (<1)	0
Cholelithiasis	1 (<1)	0
Chronic obstructive pulmonary disease	1 (<1)	0
Cold type hemolytic anemia	1 (<1)	0
Ischemic colitis	1 (<1)	0
Diaphragmatic hernia	1 (<1)	0
Diaphragmatic rupture	1 (<1)	0
Prolonged QT interval on ECG	1 (<1)	0
Autoimmune encephalitis	1 (<1)	0
Erythema nodosum	1 (<1)	0
Erythroblastosis	1 (<1)	0
Eventration repair	1 (<1)	0
Eye infection	1 (<1)	0
Febrile infection	1 (<1)	0
Femoral artery dissection	1 (<1)	0
Femur fracture	1 (<1)	0
Hemorrhagic disorder	1 (<1)	0
Hypersensitivity	1 (<1)	0
Intestinal hemorrhage	1 (<1)	0
Melena	1 (<1)	0
Musculoskeletal pain‡‡‡	1 (<1)	0
Edema§§§	1 (<1)	0
Pancreatic carcinoma	1 (<1)	0
Acute pancreatitis	1 (<1)	0
Pelvic abscess	1 (<1)	0
Perirectal abscess	1 (<1)	0
Plasma cell myeloma	1 (<1)	0
Portal hypertension	1 (<1)	0
Pyelonephritis	1 (<1)	0
Acute pyelonephritis	1 (<1)	0
Rectal abscess	1 (<1)	0
Squamous cell carcinoma	1 (<1)	0
Staphylococcal sepsis	1 (<1)	0
Thrombotic microangiopathy	1 (<1)	0
Ureteric obstruction	1 (<1)	0
Urinary retention	1 (<1)	0
Venous thrombosis/phlebitis¶¶¶	1 (<1)	0
Wound evisceration	1 (<1)	0
Myocardial infarction****	0	5 (2)

Adverse event, n (%)	Olaparib plus bevacizumab (N=535)	Placebo plus bevacizumab (N=267)
Cholecystitis	0	2 (1)
Constipation	0	2 (1)
Injection-site infection	0	2 (1)
Atrial fibrillation	0	1 (<1)
Cerebral hemorrhage	0	1 (<1)
Cerebrovascular accident††††	0	1 (<1)
Infective cholecystitis	0	1 (<1)
Gastric hemorrhage	0	1 (<1)
Hemorrhagic gastritis	0	1 (<1)
Goitre	0	1 (<1)
Impaired healing	0	1 (<1)
Incisional hernia	0	1 (<1)
Intra-abdominal fluid collection	0	1 (<1)
Leukopenia	0	1 (<1)
Lung infection	0	1 (<1)
Meningitis	0	1 (<1)
Pancytopenia	0	1 (<1)
Papillary thyroid cancer	0	1 (<1)
Paraneoplastic dermatomyositis	0	1 (<1)
Pelvic fracture	0	1 (<1)
Periarthritis	0	1 (<1)
Pilonidal cyst	0	1 (<1)
Rash	0	1 (<1)
Sinus polyp	0	1 (<1)
Small intestinal obstruction	0	1 (<1)
Tendon disorder	0	1 (<1)
Umbilical hernia	0	1 (<1)
Urinary tract infection	0	1 (<1)
Urosepsis	0	1 (<1)

CMV = cytomegalovirus; COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; URTI = upper respiratory infection

*The data include patients with anaemia, decreased haemoglobin level, decreased haematocrit, decreased red blood cell count, erythropenia, macrocytic anaemia, normochromic anaemia, normochromic normocytic anaemia, and normocytic anaemia

†The data include patients with intestinal obstruction and subileus

‡The data include patients with embolism, pulmonary embolism, vascular occlusion and transient ischaemic attack

§The data include patients with neutropenia, febrile neutropenia, neutropenic sepsis, neutropenic infection, decreased neutrophil count, idiopathic neutropenia, granulocytopenia, decreased granulocyte count, and agranulocytosis

¶ The data include patients with abdominal pain, abdominal pain lower and abdominal pain upper.

**The data include patients with thrombocytopenia, decreased platelet production, decreased platelet count, or decreased plateletcrit

††The data include patients with coronary artery disease, angina pectoris, angina unstable and Prinzmetal angina

‡‡The data include patients with dyspnoea and dyspnea exertional

§§The data include patients with cardiac failure and acute pulmonary edema

¶¶The data include patients with fistula, urogenital fistula, lymphatic fistula and anal fistula.

***The data include patients with URTI and bronchitis

†††The data include patients with intestinal perforation and appendicitis perforated

‡‡‡The data include patients with musculoskeletal pain, myalgia and musculoskeletal chest pain

§§§The data include patients with oedema, oedema peripheral and peripheral swelling

¶¶¶The data include patients with phlebitis, thrombophlebitis, deep vein thrombosis, renal vein thrombosis and venous thrombosis

****The data include patients with myocardial infarction and acute myocardial infarction

††††The data include patients with cerebrovascular accident and hemiplegia

Appendix F. Health-related quality of life

All relevant health-related quality of life data is included in the main body of the submission in Section 10.

Appendix G. Probabilistic sensitivity analyses

Table 99. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Treatment duration	14.7	11.3	15.2	Uniform
RDI				
Rucaparib	0.880	SE=0.088		Normal
Niraparib	0.805	SE=0.081		Normal
Olaparib	0.975	SE=0.098		Normal
Bevacizumab	0.975	SE=0.098		Normal

Appendix H. Literature searches for the clinical assessment

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

The objectives of the SLR were as follows:

- to identify studies assessing clinical outcomes (efficacy, and safety) of rucaparib and other comparators as a first-line maintenance strategy for patients with ovarian cancer.
- to extract, collate and assess systematically identified efficacy and safety outcomes from studies potentially relevant to the decision problem.

The specific research questions for the SLR were as follows:

- What is the clinical efficacy and safety of rucaparib and relevant comparators as a first-line maintenance therapy in randomised controlled trials (RCT) involving patients with locally advanced or metastatic OC, fallopian tube or primary peritoneal carcinomas who have responded to first-line platinum-based chemotherapy?

Sources which were used to identify relevant publications are summarized in Table 93, Table 94 and Table 95.

Table 100 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	OVID: Excerpta Medica Database	1974 to 2024 September 23	24/09/2024
Medline	OVID: Medical Literature Analysis and Retrieval System	1946 to September 23, 2024	24/09/2024
CENTRAL	Cochrane Library: Cochrane Central Register of Controlled Trials	Up to August 2024	24/09/2024
Cochrane Database of Systematic Reviews	OVID: EBM Reviews	2005 – September 18	24/09/2024

Table 101 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NICE	www.nice.org.uk	NA	08/01/2025

Source name	Location/source	Search strategy	Date of search
SMC	https://scottishmedicines.org.uk/	NA	08/01/2025
HTA International	https://www.cambridge.org/core/journals/international-journal-of-technology-assessment-in-health-care	NA	08/01/2025
Clinical trials register	https://clinicaltrials.gov/	NA	08/01/2025
International trials register	http://apps.who.int/trialsearch/	NA	08/01/2025

Abbreviations: NICE = National Institute for Health and Care Excellence; SMC = Scottish Medicines Consortium

Table 102 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ASCO	Conference website	Manual search	A combination of one or more of the following abstract search terms were used: • Ovarian cancer • Fallopian tube carcinoma • Primary peritoneal carcinomas • Fallopian tube cancer • Peritoneal cancer	08/01/2025
ESMO	Conference website	Manual search	A combination of one or more of the following abstract search terms were used: • Ovarian cancer • Fallopian tube carcinoma • Primary peritoneal carcinomas • Fallopian tube cancer	08/01/2025

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
			• Peritoneal cancer	
ISPOR	Conference website	Manual search	A combination of one or more of the following abstract search terms were used: • Ovarian cancer • Fallopian tube carcinoma • Primary peritoneal carcinomas • Fallopian tube cancer • Peritoneal cancer	08/01/2025
ESGO	Conference website	Manual search	A combination of one or more of the following abstract search terms were used: • Ovarian cancer • Fallopian tube carcinoma • Primary peritoneal carcinomas • Fallopian tube cancer • Peritoneal cancer	08/01/2025
IGCS	Conference website	Manual search	A combination of one or more of the following abstract search terms were used: • Ovarian cancer • Fallopian tube carcinoma • Primary peritoneal carcinomas • Fallopian tube cancer • Peritoneal cancer	08/01/2025
SGO	Conference website	Manual search	A combination of one or more of the following abstract search terms were used: • Ovarian cancer	08/01/2025

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
			• Fallopian tube carcinoma • Primary peritoneal carcinomas • Fallopian tube cancer • Peritoneal cancer	

Abbreviations: ASCO = American Society of Clinical Oncology; ESGO = European Society of Gynaecological Oncology; ESMO = European Society for Medical Oncology; IGCS = International Gynecologic Cancer Society; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; SGO = Society of Gynecologic Oncology

H.1.1 Search strategies

Electronic searches were designed by a medical librarian, using both indexed and free text terms.

Bibliographies of additional relevant systematic review articles were identified to obtain relevant references. Bibliographies of accepted studies were reviewed to obtain further relevant references.

Table 103 Embase (Ovid): 1974 to 2024 September 23. Date searched September 24, 2024

No.	Query	Results
Population		
1.	exp ovary cancer/ or exp ovary/ or ovary disease/	343486
2.	(ovar$ adj6 (cancer$ or neoplas$ or tumo?r$ or malignan$ or metasta$ or carcino$ or adenocarcino$ or adeno-carcino$ or onco$)).ti,ab.	174013
3.	uterine tube tumor/ or exp Fallopian tube/ or exp uterine tube disease/	15357
4.	((fallopian tube? or fallopian tubal) adj6 (neoplas$ or tumo?r$ or cancer$ or carcino$ or adenocarcino$ or adeno-carcino$ or malignan$ or metast$ or onco$)).ti,ab.	5397
5.	exp peritoneum tumor/ or exp peritoneum/	107648
6.	((periton$ adj6 (neoplas$ or tumo?r$ or cancer$ or carcino$ or adenocarcino$ or adeno-carcino$ or malignan$ or metast$ or onco$)) or (psammomacarcino$ or psammoma-carcino$)).ti,ab.	39395
7.	or/1-6	507740
Intervention		
8.	olaparib/ or rucaparib/ or niraparib/ or bevacizumab/	91347
9.	(olaparib or AZD 2281 or AZD2281 or lynparza or AZD221 or rucaparib or rubraca or PF-01367338 or AG014699 or "AG	47152

No.	Query	Results
	014699" or niraparib or MK4827 or MK 4827 or bevacizumab or avastin).ti,ab.	
10.	or/8-9	94137
11.	(maintain or maintenance or consolidat$).ti,ab,tw.	889435
Study design		
12.	exp randomized controlled trial/ or phase 3 clinical trial/ or phase 4 clinical trial/	884824
13.	(exp clinical trial/ or prospective study/) and random$.ti,ab.	881722
14.	randomization/ or single blind procedure/ or double blind procedure/ or triple blind procedure/ or placebo/	670572
15.	((singl$ or doubl$ or tripl$) adj3 (blind$3 or mask$3 or dummy)).ti,ab.	299387
16.	(random$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).ti,ab.	543896
17.	(((phase II or phase 2 or clinic$) adj3 trial$) and random$).ti,ab.	297008
18.	(placebo$ or (allocat$ adj2 random$)).ti,ab.	436832
19.	((random$ adj3 trial$) or "clinicaltrials.gov" or (systematic adj (review$ or overview$)) or meta-analy$ or metaanaly$).ti,ab.	1204082
20.	single arm.ti,ab.	33244
21.	(nonrandom$ or non random$ or quasi random$ or quasirandom$).ti,ab.	75610
22.	or/12-21	2314660
23.	7 and 10 and 11 and 22	1048
24.	animal/ or animal experiment/ or (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw.	7952348
25.	exp human/ or human experiment/	27118334
26.	24 not (24 and 25)	5912578
27.	letter/ or case study/ or (letter or editorial or note or erratum or short survey).pt.	3965247
28.	or/26-27	9770895
29.	23 not 28	1011
30.	("conference abstract" or "conference review" or "conference paper").pt. or conference$.so,st.	6067332
Clinical outcomes		
31.	29 not 30	424
32.	limit 30 to yr="2021 -Current"	1083044

No.	Query	Results
33.	29 and 32	257
34.	31 or 33	681

Searched 24/09/2024 via Ovid; Search limits: Time Period for conferences, no limits for other publications

Table 104 MEDLINE ALL (Ovid): 1946 to September 23, 2024. Date searched September 24, 2024

Search Number	Search Terms	Results
1.	exp Ovarian Neoplasms/ or exp Ovary/ or Ovarian Diseases/	195598
2.	(ovar$ adj6 (cancer$ or neoplas$ or tumo?r$ or malignan$ or metasta$ or carcino$ or adenocarcino$ or adeno-carcino$ or onco$)).ti,ab.	120460
3.	Fallopian Tube Neoplasms/ or Fallopian Tubes/ or Fallopian Tube Diseases/	17585
4.	((fallopian tube? or fallopian tubal) adj6 (neoplas$ or tumo?r$ or cancer$ or carcino$ or adenocarcino$ or adeno-carcino$ or malignan$ or metast$ or onco$)).ti,ab.	3241
5.	Peritoneal Neoplasms/ or Peritoneum/	32280
6.	((periton$ adj6 (neoplas$ or tumo?r$ or cancer$ or carcino$ or adenocarcino$ or adeno-carcino$ or malignan$ or metast$ or onco$)) or (psammomacarcino$ or psammoma-carcino$)).ti,ab.	25841
7.	or/1-6	289398
8.	Bevacizumab/	15112
9.	(olaparib or AZD 2281 or AZD2281 or lynparza or AZD221 or rucaparib or rubraca or PF-01367338 or AG014699 or "AG 014699" or niraparib or MK4827 or MK 48274827 or bevacizumab or avastin).ti,ab.	25130
10.	or/8-9	27696
11.	(maintain or maintenance or consolidat$).ti,ab,kw.	657381
12.	exp Randomized Controlled Trial/ or Clinical Trial, Phase III/ or Clinical Trial, Phase IV/	628850
13.	(exp Clinical Trial/ or Prospective Studies/) and random$.ti,ab.	542379
14.	Random Allocation/ or Single-Blind Method/ or Double-Blind Method/ or Placebos/	331705
15.	((singl$ or doubl$ or tripl$) adj3 (blind$3 or mask$3 or dummy)).ti,ab.	210635
16.	(random$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).ti,ab.	370053
17.	(((phase II or phase 2 or clinic$) adj3 trial$) and random$).ti,ab.	221441
18.	(placebo$ or (allocat$ adj2 random$)).ti,ab.	301097
19.	((random$ adj3 trial$) or "clinicaltrials.gov").ti,ab.	566799

Search Number	Search Terms	Results
20.	single arm.ti,ab.	15841
21.	(nonrandom$ or non random$ or quasi random$ or quasirandom$).ti,ab.	58480
22.	((systematic adj (review$ or overview$)) or meta-analy$ or metaanaly$).ti,ab.	489660
23.	limit 22 to yr="2018 -Current"	305029
24.	or/12-21,23	1549350
25.	7 and 10 and 11 and 24	302
26.	exp animals/ not humans/	5261218
27.	(comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case reports or historical article).pt. or Letter/ or Case Reports/	5058167
28.	or/26-27	10186377
29.	25 not 28	291

Searched 24/09/2024 via Ovid; Search limits: Time Period for conferences 2021 onwards, no limits for other publications

Table 105 CENTRAL (Cochrane Central Register of Controlled Trials. EBM Reviews) (Ovid): August 2024. Date searched: September 24, 2024

Search Number	Search Terms	Results
1.	exp Ovarian Neoplasms/ or exp Ovary/ or Ovarian Diseases/ or Fallopian Tube Neoplasms/ or Fallopian Tubes/ or Fallopian Tube Diseases/ or Peritoneal Neoplasms/ or Peritoneum/	5979
2.	(ovar$ adj6 (cancer$ or neoplas$ or tumo?r$ or malignan$ or metasta$ or carcino$ or adenocarcino$ or adeno-carcino$ or onco$)).ti,ab,kw.	8994
3.	((fallopian tube? or fallopian tubal) adj6 (neoplas$ or tumo?r$ or cancer$ or carcino$ or adenocarcino$ or adeno-carcino$ or malignan$ or metast$ or onco$)).ti,ab,kw.	1073
4.	((periton$ adj6 (neoplas$ or tumo?r$ or cancer$ or carcino$ or adenocarcino$ or adeno-carcino$ or malignan$ or metast$ or onco$)) or (psammomacarcino$ or psammoma-carcino$)).ti,ab,kw.	2710
5.	or/1-4	12747
6.	Bevacizumab/	3089
7.	(olaparib or Lynparza or rucaparib or Rubraca or niraparib or bevacizumab or avastin).ti,ab,kw.	8889
8.	or/6-7	9162
9.	(maintain or maintenance or consolidat$).ti,ab,kw.	85877
10.	5 and 8 and 9	663
11.	conference proceeding.pt.	244835
12.	10 not 11	320
13.	limit 11 to yr="2021 -Current"	51935
14.	10 and 13	136
15.	12 or 14	456

Searched 24/09/2024 via Ovid; Search limits: Time Period for conferences 2021 onwards, no limits for other publications

Table 106 CDSR (Cochrane Database of Systematic Reviews. EBM Reviews) (Ovid): 2005 to September 18, 2024. Date searched September 24, 2024

Search Number	Search Terms	Results
1.	(ovar$ adj6 (cancer$ or neoplas$ or tumo?r$ or malignan$ or metasta$ or carcino$ or adenocarcino$ or adeno-carcino$ or onco$)).ti,ab,kw.	70
2.	((fallopian tube? or fallopian tubal) adj6 (neoplas$ or tumo?r$ or cancer$ or carcino$ or adenocarcino$ or adeno-carcino$ or malignan$ or metast$ or onco$)).ti,ab,kw.	9
3.	((periton$ adj6 (neoplas$ or tumo?r$ or cancer$ or carcino$ or adenocarcino$ or adeno-carcino$ or malignan$ or metast$ or onco$)) or (psammomacarcino$ or psammoma-carcino$)).ti,ab,kw.	11
4.	or/1-3	75
5.	(olaparib or Lynparza or rucaparib or Rubraca or niraparib or bevacizumab or avastin).ti,ab,kw.	35
6.	(maintain or maintenance or consolidat$).ti,ab,kw.	534
7.	4 and 5 and 6	1
8.	(202312$ or 2024$).up.	2577
9.	7 and 8	1

Searched 24/09/2024 via Ovid; Search limits: Time Period for conferences 2021 onwards, no limits for other publications

H.1.2 Systematic selection of studies

Studies identified through the searches were evaluated for their eligibility for inclusion in the SLR using the PICOS criteria (Table 100), as described below.

The review focused on female patients with de novo locally advanced or metastatic OC, fallopian tube or primary peritoneal carcinomas who have responded to platinum-based therapy.

In studies that enrolled mixed populations of patients, where only a proportion of patients in the study meet the review inclusion criteria or populations were presented as subgroups, publications were included in the SLR if relevant outcomes data were separable for the population of interest, or if 80% or more of the study population met the above criteria.(98)

Doses and formulations of interventions (licensed and under development) being used as maintenance therapy for locally advanced and metastatic OC, fallopian tube or primary peritoneal carcinomas were be included in the review. Radiotherapy, surgery, best supportive care, chemotherapy, and placebo approaches were included only when delivered in combination with a targeted treatment, or if there was study arm in the trial containing a targeted treatment specified below (Table 100, Interventions). Interventions used only to treat the adverse effects of maintenance therapies for ovarian cancer were not included.

After the initial removal of duplicate citations, abstracts were screened by two independent investigators using the pre-specified inclusion and exclusion criteria. Any discrepancies between the two investigators were reviewed and resolved by a third investigator before the screening proceeded to review of full-text publications that had passed the first level of screening. Interventions/comparators of interest were not considered as an exclusion criterion in this initial screening phase.

The inclusion/exclusion criteria for the interventions/comparators of interest were applied during full-text screening by two independent screeners, and resolutions were resolved by a third screener. The accepted full-text articles were further validated for their suitability for inclusion during the data-extraction phase. The screening process was documented in an online literature review tool (Nested Knowledge®).

Table 107 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	Women with de novo locally advanced or metastatic OC or fallopian tube or primary peritoneal carcinomas who†: • Have platinum-sensitive‡ disease • Have responded to first-line platinum therapy	Women in the following categories: • Early OC (stage I) • Without previous platinum-based chemotherapy+ • Prior maintenance treatment • With central nervous system metastasis that remains untreated	NA
Intervention/ Comparators	Interventions • Targeted treatments • PARP inhibitors (e.g., rucaparib, olaparib, niraparib) • Monoclonal antibodies (bevacizumab) Comparators • Targeted treatments • PARP inhibitors (e.g., rucaparib, olaparib, niraparib) • Monoclonal antibodies (bevacizumab) • Chemotherapy (platinum-based and non-platinum-based)	• Non-pharmacologic treatments, such as surgery or radiotherapy alone • Alternative doses, schedules, or formulations of the intervention as the only comparator arms	NA

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
	• No treatment/placebo/ "wait-and-see" approach • Best supportive care		
Outcomes	Efficacy • Overall survival • Progression free survival using RECIST criteria • Progression free survival on the subsequent line of treatment. • Time to progression to first treatment, • Time on treatment • Time to treatment discontinuation • Overall response rate • Duration of response Safety/ tolerability • Any adverse event • Adverse events by grade • Discontinuation due to adverse events • Including tolerability for dose. Humanistic burden • HRQoL and PROs, including symptom assessment (for example, FACT-O, FOSI, and TOI)	• Publications that do not report data on relevant outcomes • Publications that report only interim trial results	NA
Study design/publication type	• RCTs in any country (phases II/III) for efficacy, safety, and PROs	Study designs: • Non-randomised, single-arm, or observational (non-interventional)	NA

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
	• Systematic reviews and meta-analyses of RCTs	studies for efficacy, safety, PROs • Open-label extension phases of RCTs • Pre-clinical studies (animal, in vitro) • Case reports, expert opinion articles, letters, narrative (non-systematic reviews) Publications of the following types: • Narrative publications • Review articles • Case studies • Case reports • Editorials	
Language restrictions	English-language articles/conference abstracts only	Journal articles and conference abstracts without English full text	NA
Timeframe	2021 onwards for conference abstracts. No time restrictions for other publications		NA

*These criteria were formulated to ensure systematic identification of studies in line with the decision problem and the objectives and research question of the SLR. To be eligible for inclusion, studies had to meet all the inclusion criteria and therefore provide outcome data of interest for relevant interventions/comparators used in the target population. By contrast, a study meeting any of the exclusion criteria would not provide data suitable for inclusion in the review.

†In studies that enrolled mixed populations of patients, where only a proportion of patients in the study meet the review inclusion criteria or populations were presented as subgroups, publications were included in the SLR if relevant outcomes data were separable for the population of interest, or if 80% or more of the study population meet the above criteria. The threshold of 80% was selected as it is commonly used in evidence reviews supporting NICE clinical guidelines and it is recommended in the IQWIG methods (https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-2.pdf)

‡Defined as disease progression greater than six months after completion of their penultimate platinum regimen (from last dose)

FACT-O, Functional Assessment of Cancer Therapy—Ovarian; FOSI, FACT/NCCN Ovarian Symptom Index; IQWiG, The Institute for Quality and Efficiency in Healthcare; NA, not applicable; OC, ovarian cancer; PARP, poly adenosine diphosphate ribose polymerase; PICOS, Patients, interventions, comparators, outcomes, study type; PROs, Patient reported outcomes; RCT, randomised controlled trial; TOI, Trial Outcome Index

H.1.3 Excluded fulltext references

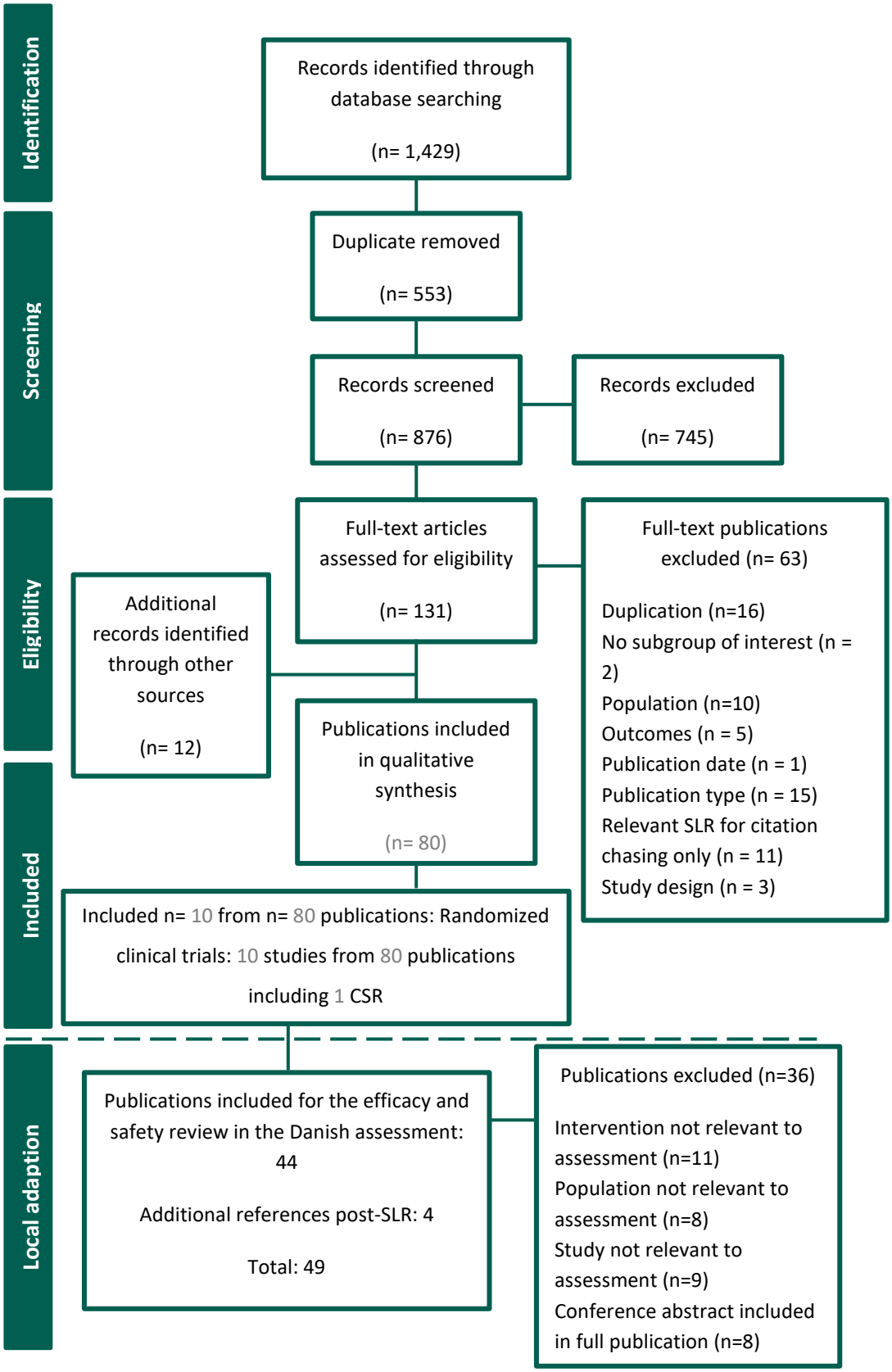
Following the SLR searches and the initial removal of duplicate citations from the search yield, there were 876 citations. Of these, 745 citations were excluded at the abstract level. Among the 131 citations remaining, 63 were rejected following further application of the inclusion/exclusion criteria to full-text citations. Additionally, 12 publications were identified via grey literature searches. Therefore, in total 80 citations that corresponded to ten unique trials were identified for inclusion in the review.

The findings from the SLR are presented for the following patient populations:

- Women with de novo locally advanced or metastatic ovarian cancer or fallopian tube or primary peritoneal carcinomas who:
  - Have platinum-sensitive disease
  - Have responded to first-line platinum therapy

Figure below illustrates the study-selection process.

Figure 40 PRISMA flow diagram of included/excluded studies: searches conducted September 24, 2024



H.1.4 Quality assessment

This systematic review followed widely accepted methodology as per the Cochrane Guidelines, and consequently was conducted to a high standard. One of the potential limitations of the methodology was the inclusion of a facet in the search strings to specify “maintenance”, in order to focus the review to articles which were most relevant. The inclusion of this facet could have resulted in studies being overlooked which did not explicitly mention one of the “maintenance terms in the title or abstract. However, comprehensive grey literature searches were conducted of conference abstracts and other HTA websites, as well as review of citations from recently published SLRs; we believe that this enabled us to capture all studies of interest despite this limitation in the search strategy.

Quality assessment of the RCTs included in the SLR was conducted using the Cochrane Risk of Bias Assessment Tool 2.0 (99). This assessment will summarise the risk of bias in the findings of randomised trials by considering five domains of potential bias: (1) bias arising from the randomisation process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcome, and (5) bias in selection of the reported result. This version of the tool also considers outcome-specific bias—given that some outcomes have no or little room for judgement (e.g., all-cause mortality) and others have considerable room for judgement (e.g., assessment of depression scores)—and assesses different outcomes separately. An overall risk of bias judgement was assigned to each outcome assessed in each trial, using the following categories: Low risk of bias, Some concerns, or High risk of bias.

Only studies available in full text underwent a quality assessment, because of the lack of details available for assessment from abstracts and posters.

Table 108 Quality assessment of clinical trials using Cochrane Collaboration Risk of Bias for RCTs Tool (RoB 2.0)

Risk of bias assessment (RoB 2.0)	ATHENA-MONO	PRIMA	PAOLA-1
Randomization process	Low	Low	Low
Deviations from the intended interventions	Low	Low	Low
Missing outcome data	Low	Low	Low
Measurement of the outcome	Low	Low	Low
Selection of the reported result	Low	Low	Low
Overall risk of bias	Low	Low	Low

H.1.5 Unpublished data

Not applicable

H.1.6 Publications update

The SLR included in this application was used to inform the ITC presented. Since completion of the SLR, 4 new articles were published providing updated efficacy and/or safety from the ATHENA-MONO trial for rucaparib.

Kristeleit R, O'Malley D, Lim MC, et al. Interim post-progression data and updated survival in patients with newly diagnosed advanced ovarian cancer in ATHENA-MONO. Gynecologic Oncology. 2024(40)

Ghamande S, Miller R, Solovyeva E, et al. ATHENA-MONO Post-Progression Survival Data Update In Patients With Newly Diagnosed Advanced Ovarian Cancer. International Journal of Gynecological Cancer. 2025(44)

Lorusso D, Kristeleit R, O'Malley D, et al. RUCAPARIB MAINTENANCE TREATMENT IN PATIENTS (PTS) WITH NEWLY DIAGNOSED OVARIAN CANCER (OC): DEFINING BENEFIT ACCORDING TO DISEASE RISK SUBGROUPS WITHIN THE PHASE 3 ATHENA-MONO STUDY. International Journal of Gynecological Cancer. 2024(52)

Kristeleit, R. S., Ghamande, S., Lisyanskaya, A. et al. Rucaparib maintenance for newly diagnosed advanced ovarian cancer: interim overall survival, progression-free survival, and safety at 5 years of follow-up from the phase III ATHENA-MONO/GOG-3020/ENGOT-ov45. Annals of Oncology. 2025(53)

Appendix I. Literature searches for health-related quality of life (N/A)

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

Not Applicable

Table 109 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Embase.com		dd.mm.yyyy
Medline	Ovid		dd.mm.yyyy
Specific health economics databases [1]			dd.mm.yyyy

Abbreviations:

Table 110 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
CEA Registry	Tufts CEA - Tufts CEA		dd.mm.yyyy

Table 111 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	e.g. conference website	Electronic search	List individual terms used to search in the congress material:	dd.mm.yyyy

[1] Papaioannou D, Brazier J, Paisley S. Systematic searching and selection of health state utility values from the literature. Value Health. 2013;16(4):686-95.

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
	Journal supplement [insert reference]	Skimming through abstract collection		dd.mm.yyyy

I.1.1 Search strategies

Table 112 Search strategy for [name of database]

No.	Query	Results
#1		88244
#2		85778
#3		115048
#4		7011
#5		10053
#6		12332
#7		206348
#8		211070
#9	#7 OR #8	272517
#10	#3 AND #6 AND #9	37

Literature search results included in the model/analysis:

I.1.2 Quality assessment and generalizability of estimates

I.1.3 Unpublished data

Appendix J. Literature searches for input to the health economic model (N/A)

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

Not applicable.

J.1.1 Example: Systematic search for […]

Table 51 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	e.g. Embase.com	e.g. 1970 until today	dd.mm.yyyy
Medline			dd.mm. yyyy
CENTRAL	Wiley platform		dd.mm. yyyy

Abbreviations:

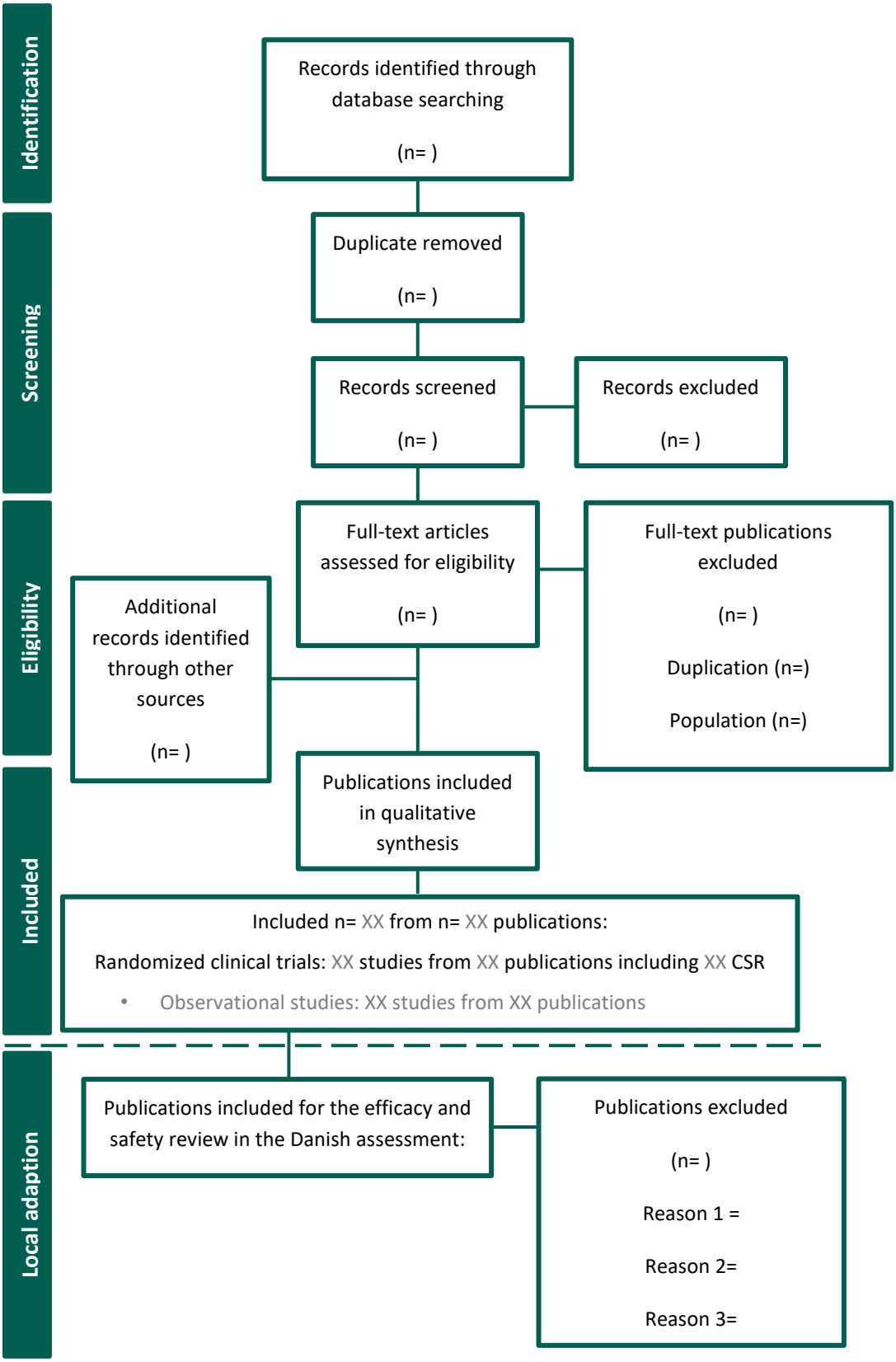
J.1.2 Example: Targeted literature search for [estimates]

Table 52 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
			dd.mm.yyyy

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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