Darolutamide with androgen deprivation therapy for treating non-metastatic hormone-relapsed prostate cancer [ID1443]

Produced by Aberdeen HTA Group

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Date completed: 12 May 2020

Version: Draft Report

Source of funding: This report was commissioned by the NIHR Systematic Reviews Programme as project number **131282.**

Declared competing interests of the authors

No competing interests to disclose.

Acknowledgements

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This report should be referenced as follows:

Scotland G, Kennedy C, Imamura M, Cooper D, Robertson C, Booth C, Vadiveloo T, Manson P, Urquhart G, Brazzelli M. Darolutamide with androgen deprivation therapy for treating non-metastatic hormone-relapsed prostate cancer [ID1443]. Aberdeen HTA Group, 2020.

Contribution of authors

Mari Imamura and Clare Robertson summarised and critiqued the company's definition of the decision problem and the clinical effectiveness evidence reported within the company submission. David Cooper with assistance from Thenmalar Vadiveloo critiqued the statistical methods and analyses presented in the company submission and checked all the numerical results related to the review of the clinical effectiveness evidence. Graham Scotland with assistance from Charlotte Kennedy and Corinne Booth critiqued the cost-effectiveness evidence submitted by the company, checked their economic model, and conducted further sensitivity analyses. Paul Manson critiqued the methods used for identifying relevant studies and checked the search strategies presented in the company submission. Gordon Urquhart provided clinical advice during the appraisal. Miriam Brazzelli coordinated all aspects of the appraisal and acted as lead for the clinical effectiveness side of the appraisal. Graham

Scotland acted as lead for the cost-effectiveness side of the appraisal. All authors contributed to the writing of this report and approved its final version.

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List of abbreviations

ADT	Androgen deprivation therapy
AE	Adverse event
AIC	Akaike information criterion
BIC	Bayesian information criterion
BPI-SF	Brief Pain Inventory Short-Form
BSC	Best supportive care
CHMP	Committee for Medicinal Products Human Use
CI	Confidence interval
CNS	Central nervous system
CRPC	Castration-resistant prostate cancer
CTCAE	Common Terminology Criteria for Adverse Events
CS	Company submission
ECOG	Eastern Cooperative Oncology Group
ERG	Evidence Review Group
EORTC-QLQ-PR25	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D-3L	EuroQol 5-dimensions 3-levels
ERG	Evidence review group
EPAR	European Public Assessment Report
FACT-P	Functional Assessment of Cancer Therapy-Prostate
HR	Hazard ratio
HRQOL	Health-related quality of life
HRPC	Hormone-relapsed prostate cancer
ICER	Incremental cost-effectiveness ratio
KM	Kaplan Maier
MFS	Metastasis-free survival
NICE	National Institute of Health and Clinical Excellence
nmCRPC	Non-metastatic castration-resistant prostate cancer
nmHRPC	Non-metastatic hormone-relapsed prostate cancer
OS	Overall survival

PAS	Patient access scheme
PCWG2	Prostate Cancer Working Group 2
PFS	Progression-free survival
PSA	Prostate-specific antigen
PSADT	Prostate-specific antigen doubling time
QALY	Quality adjusted life year
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SRE	Skeletal-related event
SSE	Symptomatic skeletal event
TEAE	Treatment-emergent adverse event
TOT	Time on treatment

1 Executive summary

1.1 Critique of the decision problem in the company's submission

The company (Bayer) provided clinical and cost effectiveness evidence for darolutamide (NEBECA®) combined with androgen deprivation therapy (ADT) for the treatment of non-metastatic hormone-relapsed prostate cancer in adults.

As highlighted in Section 2.3 of this report, the decision problem addressed by the company is aligned with the final scope issued by NICE, with a few differences as summarised in Table 1 below.

Table 1. Differences in final scope issued by NICE and decision problem addressed by the company

Parameter	Final scope issued by NICE Decision problem	Decision problem
Population	Adults with non-metastatic hormone-relapsed prostate cancer	The company addressed a narrower population than that specified in the NICE final scope and focused on non-metastatic castration-resistant prostate cancer who were at high risk of developing metastases. The company defines high risk as an absolute prostate specific antigen (PSA) level ≥2 ng/mL and a PSA doubling time (PSADT) of ≤10 months. For purpose of this submission, castration-resistant prostate cancer and hormone-relapsed prostate cancer are considered interchangeable.

1.2 Summary of the key issues in the clinical effectiveness evidence

Overall, the ERG considers the methods used to conduct the company's systematic review of clinical effectiveness evidence to be satisfactory and in line with current methodological standards (Section 3.1 of this report).

The key clinical effectiveness evidence presented by the company consists of the ARAMIS trial, a well-designed, good quality multicentre, phase III RCT comparing

darolutamide plus ADT (N = 955) with placebo plus ADT (N = 544) [Section 3.2.1 of this ERG report]. Endpoints assessed in the ARAMIS trial included metastasis-free survival (MFS) , overall survival (OS), time to pain progression, time to initiation of first cytotoxic chemotherapy, time to first symptomatic skeletal event, progression-free survival, time to PSA progression, and health-related quality of life.

The ERG considers that most of the characteristics of the patients enrolled in the ARAMIS trial are typical of patients with non-metastatic castrate-resistant prostate cancer (nmCRPC), who would be seen in clinical practice in the UK [Section 3.2.1 of this ERG report].

The ERG has some doubts on whether the proportions of patients receiving subsequent therapies in the ARAMIS trial could be generalisable to those who would be seen in UK clinical practice. In particular, the ERG's clinical expert is of the opinion that ARAMIS includes a higher proportion of participants receiving docetaxel, and a lower proportion receiving enzalutamide and abiraterone, than would be expected in current clinical practice. This could confound the OS results in favour of darolutamide.

The ARAMIS trial showed that darolutamide was associated with a significant improvement in MFS compared with placebo with a median MFS of 40.4 months in the darolutamide plus ADT arm, compared with 18.4 months in the placebo + ADT arm (HR 0.41, 95% CI [0.34, 0.50], $p<0.001$). The MFS benefit was maintained across all subgroup analyses. Results of the secondary endpoints as well as of exploratory endpoints further support the clinical benefit of darolutamide over placebo.

In the ARAMIS trial incidence and pattern of treatment-emergent adverse events (TEAEs) were broadly similar in the darolutamide and placebo arms. Darolutamide was associated with higher rates of fatigue, rash and cardiac disorders. Most common events leading to treatment discontinuation were cardiac failure and death.

Key points of clinical effectiveness and safety evidence

- The ERG is happy with the methods used in the CS and agree that the ARAMIS data indicate a benefit on the primary outcome of MFS for those receiving darolutamide plus ADT compared with those receiving ADT alone. The clinical benefit of darolutamide is further supported by the results of the secondary and explanatory endpoints.

- The ERG is questioning whether the benefit on OS from darolutamide shown in the ARAMIS trial is generalisable to UK clinical practice. While the updated analysis (Nov 2019 data–cut) does have a sufficient number of events, the majority of participants are still contributing a censored survival time. The ERG is also of the opinion that the benefit shown in the ARAMIS trial may be affected by the fact that only half of participants who discontinued the study treatment received a subsequent treatment. Moreover, in the ARAMIS trial the proportions of patients who received subsequent treatments are not entirely in line with those observed in the UK clinical practice.
- The proportion of subsequent treatments used in the ARAMIS trial differ from those that the company has used in their economic model.
- The ERG also has concerns that the subgroup analyses presented by the company on overall survival suggests that any beneficial effect is restricted to a specific population and that those younger than 65 or those from the Asia Pacific region or those of Asian ethnic origin may not experience the same benefit.
- While the likelihood of certain special adverse events is increased for those receiving darolutamide, the ERG does not have any particular concern regarding the safety profile of darolutamide.

1.3 Summary of the key issues in the cost effectiveness evidence

The company submitted a partitioned survival model comparing darolutamide plus ADT with ADT alone. The company used parametric survival curves for MFS and OS, fitted independently to the observed data by treatment arm in the ARAMIS trial, to partition the cohort between nmCRPC, mCRPC and death. A 28-day cycle length was used. Time on treatment (ToT) data from the darolutamide arm of ARAMIS were extrapolated to determine the expected proportion of patients on and off treatment in

the nmCRPC health state. Patients discontinue darolutamide upon progression to mCRPC, but can also discontinue for other reasons prior to progression.

The mCRPC health state captures patients receiving first-, second- and third-line treatments and best supportive care. Metastatic progression is included as a single health state in the model but the costs associated with each line of treatment are estimated separately and a single weighted-average utility value is applied to both arms based on the time spent on each line of treatment. The post-progression treatment pathways applied in each arm of the model were derived from clinical expert opinion, rather than the proportions observed in the ARAMIS trial, to better reflect current UK NHS practice.

The ERG believes the following to the be the key issues and uncertainties in the cost-effectiveness evidence:

1. The model structure, which collapses up to three lines of subsequent active therapy into a single mCRPC health state, leads to some uncertainty around progressed health state utility and subsequent treatments costs. Whilst the ERG believes the company has provided a reasonable approximation in the context of the Part-SA model, the complexity of the treatment pathway might be better accommodated using a Markov state transition model reflecting the relationship between progression and mortality risk, and the efficacy of subsequent treatments available to patients in the progressed state. However, the ERG acknowledges that previous committee opinion in TA580 has influenced their decision to adopt the partitioned survival approach.
2. The company updated their OS and ToT curves to a latter November 2019 data cut at the clarification stage, but retained the MFS curves from the earlier September 2018 data cut in their revised base case. The ERG is concerned that combining curves from different data cuts generates additional uncertainty, particularly with respect MFS and ToT, where the update has resulted in greater divergence between these curves, greatly reducing the darolutamide treatment costs in the nmCRPC health state.

3. The generalisability of the ARAMIS trial OS benefit for darolutamide plus ADT versus ADT alone, to the modelled NHS treatment pathway. This is because subsequent treatments in the ARAMIS differed from the suggested subsequent treatment distribution in NHS routine clinical practice.
4. Related to the point 3, The ERG believes the OS extrapolation for darolutamide plus ADT may be overoptimistic, leading to a life-year (LY) and quality-adjusted life-year (QALY) gain that lacks face validity. In particular, the ERG questions the face validity of patients in the darolutmide arm accruing more undiscounted life years in the mCRPC health state compared to patients in the ADT arm, when patients in the ADT arm have greater access to subsequent treatments that have been shown in previous trials and appraisals to increase OS in the mCRPC health state. The mechanism driving this, is an ever increasing proportional reduction in the hazard of mortality in the darolutamide arm compared to the ADT arm.
5. The monitoring costs applied to the nmCRPC and mCRPC health states are based on a small sample of NHS patients recruited over a relatively wide time interval (2011 – 2019), and some elements of resource use frequency appear low compared to estimates previously accepted in relevant submissions (e.g. TA580 and TA377).

1.4 Summary of ERG's preferred assumptions and resulting ICER

The ERG's preferred assumptions are as follows:

- Given the relative immaturity of the OS data from the ARAMIS trial (median OS not reached), and uncertainty regarding the generalisability of the OS benefit and the long-term extrapolations (points 3 and 4 above), the ERG prefers scenarios that equalise the hazards of mortality from a future timepoint beyond the trial follow-up period. The ERG acknowledges that selection of a cut-off for the relative mortality benefit is somewhat arbitrary, but are guided by their clinical expert's expectation that OS would be zero by 20 years in both arms. Further, the ERG believes the selection should result in undiscounted mCRPC life years being greater in the ADT arm of the model. Five years is applied in the ERG base case, and seven years is also tested.

- Since updating of darolutamide ToT analysis resulted in a downward shift in the curve (due to more censoring events being replaced with discontinuation events), and MFS was not updated to the corresponding data cut, the ERG prefer to adopt a more pessimistic extrapolation of MFS. This assumes a similar downward shift in the MFS curve might have been observed had it also been updated to the same data cut. To account for this, the Gompertz curve is selected for both treatment arms. The ERG acknowledges the uncertainty in this revision, and suggest that this uncertainty would be better addressed by updating MFS to the same data cut as ToT and OS.
- Application of the health care resource use estimates from TA580.
- Application of revised end of life costs, ADT administration costs, and oncology outpatient visit costs (rather than the PSSRU average outpatient unit cost).

With these combined changes, the deterministic ICER for darolutamide plus ADT versus ADT alone comes to £8,429 per QALY gained (Table 2). These results include the PAS discount for darolutamide and Radium-223, but do not include available discounts for other subsequent therapies.

Table 2. ICER resulting from ERG's preferred assumptions

	Total costs	Total QALYs	Δ costs	Δ QALYs	ICER £/QALY
Darolutamide plus ADT	[redacted]	[redacted]			
ADT alone	[redacted]	[redacted]	£3,887	0.46	£8,429

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

As a result of the issues identified above, the ERG explored scenarios with alternative curve extrapolations, including: equalized hazards of mortality between the treatment arms from 7 years; and a Weibull extrapolation of the Nov 2019 ToT curve (in combination with the Gompertz extrapolation of the Sept 2018 MFS data). In general,

the ICER increases with scenarios that reduce the OS benefit, and reduce the difference between the selected MFS and ToT curves for darolutamide.

Table 3. Scenario analyses undertaken on the ERG base case

Description	Darolutamide + ADT			ADT alone			
	Costs	QALY	LYG	Costs	QALY	LYG	ICER vs ADT
ERG base	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,429
Equalise mortality to ADT arm from 7 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,819
Average of Nov 2019 generalised gamma and Weibull for darolutamide OS, instead of equalising mortality from 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,318
Weibull extrapolation of Nov 2019 darolutamide ToT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,748

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The relevant health condition for this submission is non-metastatic hormone-relapsed prostate cancer (nmHRPC), referred to in the company submission (CS) as non-metastatic castration-resistant prostate cancer (nmCRPC). The company's description of nmCRPC in terms of prevalence, symptoms and complications appears generally accurate and in keeping with the decision problem. The relevant intervention for this submission is darolutamide (NUBEQA®).

2.2 Background

Prostate cancer is the 3rd most common cause of cancer death for males and females combined in the UK, accounting for 7% of cancer deaths, with 10,146 prostate cancer-related deaths in England in 2017,[3] and provisional data indicate that prostate cancer was the most common cancer diagnosis in England, with around 49,000 new prostate cancer cases diagnosed in 2018.[4] People who receive an early diagnosis of prostate cancer are likely to have a 5-year survival rate of 100%, whereas the 5-year survival rate for people who are diagnosed at advanced stages of the disease is 49%. Advanced stage disease is associated with symptoms including urinary outflow obstruction, urinary urgency or frequency and haematuria.[3] Advanced disease is also associated with metastases, mainly to the lymph nodes, bone or visceral sites, and can cause multiple complications such as bone pain, pathologic fractures and skeletal-related events (SREs) such as spinal cord compression.[5] Metastatic disease is also a cause of death in people with prostate cancer.[6]

Stages of prostate cancer are classified based on responsiveness to hormonal therapy (i.e. responsiveness to androgen deprivation therapy [ADT] or surgical castration) and the extent of the disease as localised, locally advanced or metastatic. Many patients with early stage or non-metastatic disease will receive localized treatment such as radical prostatectomy and/or radiotherapy, and/or ADT. Patients who relapse after surgery or radiotherapy may also receive ADT but nearly all will eventually become resistant to ADT and develop progressive disease, known as castration resistant prostate cancer (CRPC) or hormone-relapsed prostate cancer (HRPC).[7] Around 15% of new prostate cancer cases are CRPC and 16% of these are nmCRPC. Patients with nmCRPC are usually asymptomatic but are at risk of progression to

metastatic disease, and consequently shortened survival, increased pain, and reduced quality of life. nmCRPC patients with shorter prostate specific antigen (PSA) doubling time (PSADT) of 10 months or less, and increasing PSA levels and/or PSA velocity are at even higher risk of developing metastases. Metastatic disease is also associated with increased use of healthcare resources and increased healthcare costs.[8] It is estimated that 33% of nmCRPC patients will develop metastases within 2 years of diagnosis.[9] Delaying the development of metastases is, therefore, a key aim of treatment for patients with nmCRPC. The company present a schematic representation of the evolutionary patterns of nmCRPC in Figure 1, Document B, of the CS.

The company provides details of international guideline recommendations for the treatment of nmCRPC in Table 3, Document B, of the CS. While NICE guideline 131 provides guidelines for the treatment and active surveillance of local and locally advanced disease, there is currently no specific guidance for the monitoring or treatment of patients with nmCRPC in the UK.[10] The company notes that clinical evidence suggests that second generation androgen receptor inhibitors (ARI) give significantly longer metastases-free survival (MFS) when added to ADT, but also notes that enzalutamide is not currently recommended by NICE for treating high-risk nmCRPC and the NICE appraisal of apalutamide is suspended at the time of this CS. The company state that darolutamide is a non-steroidal ARI that differs structurally to enzalutamide and apalutamide, and offers the potential for fewer and less severe toxic central nervous system (CNS) related effects due to its low penetration of the blood brain barrier and low binding affinity for y-aminobutyric acid type A ($GABA_A$) receptors.[11, 12] The company propose that darolutamide would be used in conjunction with ADT as first line treatment for nmCRPC patients who are at high risk of developing metastatic disease. The company also cites expert opinion that the use of darolutamide in this setting is likely to change the treatment patterns of other ARIs once patients progress to metastatic disease.[13] The company outlines the current and proposed treatment pathway for nmCRPC patients in Figure 3, Document B, of the CS and this is reproduced by the ERG as Figure 1. The ERG agrees with the company's outline of the current treatment pathway in the UK and the proposed positioning of darolutamide and subsequent treatment options.

	Current UK situation	After Darolutamide nmCRPC approval
nmCRPC	ADT	Darolutamide + ADT
mCRPC	Following progression to metastases (% of patients receiving each treatment)	
1st line options*:	Abiraterone +ADT (40-42.5%) Enzalutamide + ADT (40-42.5%) Docetaxel + ADT (10-15%) No treatment / BSC (2-5%) Radium-223 + ADT^ (0-3%)	Docetaxel + ADT (55-60%) Radium-223 + ADT^ (20%) No treatment / BSC (15-20%) Abiraterone +ADT (1-5%)
2nd line options*:	Docetaxel + ADT (50%) Radium-223 + ADT^ (15-20%) No treatment / BSC (15%) Abiraterone +ADT (5-7.5%) Enzalutamide + ADT (5-7.5%) Cabazitaxel + ADT (1-5%)	No treatment / BSC (25-50%) Cabazitaxel + ADT (20-30%) Radium-223 + ADT^ (20%) Docetaxel + ADT (5-15%) Abiraterone +ADT (1-10%)
3rd line options*:	No treatment / BSC (45-50%) Cabazitaxel + ADT (20-30%) Radium-223 + ADT^ (20%) Docetaxel + ADT (5%) Abiraterone +ADT (0-5%) Enzalutamide + ADT (0-5%)	No treatment / BSC (80%) Cabazitaxel + ADT (10%) Radium-223 + ADT^ (5-10%) Abiraterone + ADT (0-5%)

Figure 1. The company's current and proposed treatment pathway for patients with nmCRPC

ADT=androgen deprivation therapy; BSC=best supportive care; mCRPC=metastatic castration-resistant prostate cancer; nmCRPC= non-metastatic castration-resistant prostate cancer

2.3 Critique of company's definition of decision problem

A summary of the company's decision problem in relation to the NICE final scope is presented in Table 4. A critique of how the company's economic modelling adheres to the NICE reference case is provided in Chapter 4.

Table 4. Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	Adults with non-metastatic hormone-relapsed prostate cancer	Adults with non-metastatic castration-resistant prostate cancer who are at high risk of developing metastatic disease	Aligned with expected wording of the marketing authorization and evidence from the pivotal trial, ARAMIS	The CS addresses a narrower population than that specified in the NICE final scope and focuses on adults with high-risk nmCRPC. The company defines high risk as an absolute prostate specific antigen (PSA) level ≥2 ng/mL and a PSA doubling time (PSADT) of ≤10 months. For purpose of this submission, nmCRPC and nmHRPC are considered interchangeable. The ERG believes that the narrowing of population definition to high risk nmCRPC is appropriate for the decision problem. High-risk nmCRPC is the anticipated license indication for darolutamide and is in line with the study population in the clinical evidence (ARAMIS). This sub-population ('high risk') definition was also used in previous NICE technology appraisals for the same disease indication (nmCRPC) including enzalutamide (TA580).[14] According to the views of an expert panel of oncologists consulted by the company (Bayer Meeting Report), as well as that of the ERG's clinical advisor, the definition of a high-risk patient population used in the CS matches that of patients seen in UK clinical practice.[13]

Intervention	Darolutamide + ADT	Darolutamide + ADT	Not applicable	The intervention described in the CS matches that described in the NICE final scope. Darolutamide is administered as oral dose of 600 mg twice daily, equal to a total daily dose of 1200 mg. It is proposed that darolutamide would be used with androgen deprivation therapy (ADT) as first line treatment for patients with nmCRPC at high risk of developing metastases. The company states that darolutamide would be prescribed and used in the clinical practice in the same way as in the ARAMIS trial in terms of dose, administration and indication. The Committee for Medicinal Products Human Use (CHMP) granted a positive opinion on 30 January 2020 and the European Commission decision was expected at the end of March 2020 at the time of the CS.[15] Following the preparation of the CS, darolutamide (NUBEQA®) received a marketing authorisation for CRPC at high risk of metastasis on 27 March 2020 and the final European Public Assessment Report (EPAR) was published on 1 April 2020 (https://www.ema.europa.eu/en/medicines/human/EPAR/nubeqa).
Comparator(s)	Androgen deprivation therapy	Androgen deprivation therapy	Not applicable	The comparator described in the CS matches that described in the final scope. While at present in the UK there is no specific guidance for the monitoring or management of people with nmCRPC, the current NICE guidelines for prostate cancer provides recommendations for active surveillance of men with localised disease.[10]

				The defined comparator (ADT) aligns with current management of nmCRPC patients in the UK and in line with international prostate cancer guidelines including European Association of Urology (EAU)[16], American Urological Association (AUA)[17] and National Comprehensive Cancer Network (NCCN).[18]
Outcomes	The outcome measures to be considered include: • Metastasis-free survival • Time to prostate-specific antigen progression • Overall survival • Adverse effects of treatment • Health-related quality of life	As per final scope	Not applicable	The outcomes in the company's submission matches the outcomes described in the final scope. The standard clinical outcome used in oncology clinical trials has been overall survival. The use of metastasis-free survival as a surrogate for overall survival and as a primary endpoint in therapies for nmCRPC was recognised by the US Food and Drug Administration (FDA) Oncologic Drugs Advisory Committee.[19] In the ARAMIS trial, the key source of evidence submitted by the company, the median OS was not reached at the time of data cut-off for the primary analysis (3rd September, 2018). Since the preparation of the CS, the final OS analysis cut-off has been reached (15th November, 2020) and the results have been supplied to the ERG at clarification.
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year	Incremental cost per quality-adjusted life year gained analysis	Not applicable	In line with the NICE final scope.

Subgroups	No subgroups specified	Not specified	Not applicable	No subgroups were specified in the final scope issued by NICE.
Special considerations including issues related to equity or equality	No special considerations specified	Not specified	Not applicable	The ERG agrees with the company that there are no anticipated equality issues related to darolutamide.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

Full details of the methods used to identify and select the clinical evidence relevant to this appraisal are reported in Appendix D.1 of the CS. The ERG appraisal of the company's systematic review methods is summarised in Table 5 below.

Table 5. ERG appraisal of the systematic review methods presented in the CS

Review process ERG	ERG response	Comments
Were appropriate searches (e.g., search terms, search dates) performed to identify all relevant clinical and safety studies?	Yes	Details provided in Appendix D.1 of the CS.
Were appropriate bibliographic databases/sources searched?	Yes	Sources included MEDLINE, Embase, CENTRAL, The Cochrane Library and searches of trial registries for identification of ongoing trials and of conference proceedings of relevant international clinical meetings. See Appendix D.1 of the CS.
Were eligibility criteria consistent with the decision problem outlined in the NICE final scope?	Yes	See Appendix D.1 of the CS.
Was study selection conducted by two or more reviewers independently?	Yes	See Appendix D.1 of the CS.
Was data extraction conducted by two or more reviewers independently?	Possibly	In Appendix D.1 of the CS, it is stated one reviewer extracted the data and all extracted data were 'quality checked' by a second reviewer.
Were appropriate criteria used to assess the risk of bias of identified studies?	Yes	See Table 8, Appendix D.3 of the CS.
Was risk of bias assessment conducted by two or more reviewers independently?	Possibly	One reviewer performed the 'risk of bias' assessment, which was checked by a second reviewer against the source publication (Bayer

		response to Question A1 of the clarification document).
Was identified evidence synthesised using appropriate methods?	Not applicable	As the SLR identified only one RCT, meta-analysis was not conducted.

Overall, the ERG considers the methods used by the company to conduct the systematic review of clinical effectiveness evidence in line with current methodological standards.

The ERG conducted a quality assessment of the methods used by the company for the systematic review of clinical evidence using the Centre for Review and Dissemination (CRD) criteria; results are presented in Table 6.

Table 6. Quality assessment of the company's systematic review of clinical effectiveness evidence

CRD quality item	Yes/No/Unclear
1. Are any inclusion/exclusion criteria reported relating to the primary studies, which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all of the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included study

The evidence for the clinical efficacy and safety of darolutamide (NEBECA®, Bayer) for adults with nmCRPC (non-metastatic castoration-resistant prostate cancer) consists of one multicentre, randomised placebo-controlled Phase III clinical trial, ARAMIS.[1] An overview of the study is presented in Table 4, Section B.2.2 of the CS. Study methods are summarised in Section B.2.3 and the participant flow of the study is presented in Figure 2, Appendix D.2 of the CS.

ARAMIS was sponsored by Bayer HealthCare and Orion Pharma and investigated the efficacy of darolutamide for men with nmCRPC who were at high risk of developing metastases. High risk was defined as an absolute prostate specific antigen (PSA) level of ≥2 ng/ml and a prostate specific antigen doubling time (PSADT) of 10 months or less. Participants had CRPC with undetectable metastases by conventional imaging techniques (i.e. computed tomography, magnetic resonance imaging or bone scan).

ARAMIS assessed darolutamide (oral dose of 600 mg twice daily, equal to a total daily dose of 1200 mg) versus placebo. A total of 1,509 men (median age = 74 years) were randomised in a 2:1 ratio to receive either oral darolutamide plus androgen deprivation therapy (ADT) [N = 955] or matched oral placebo plus ADT [N = 554]. The use of osteoclast-targeted therapy was allowed for the treatment of osteoporosis (reported for [redacted] and [redacted] of patients at randomisation, for the darolutamide and placebo groups, respectively) and was a stratification factor (yes or no) during randomisation.[20] Randomisation was also stratified according to PSADT (≤6 months or >6 months).

Participants remained on study drug until confirmed metastasis (protocol-defined progression), an intolerable adverse event (AE) or withdrawal of consent. As of the data cut-off date for the primary analysis (3rd September 2018), the median follow-up time from randomisation to the last contact or death was 17.9 months ([redacted] months [redacted] months] for darolutamide and [redacted] months [redacted] months] for placebo). The study was conducted in 36 countries worldwide in 409 centres, including [redacted] centres in the UK. Although the study enrolled [redacted] patients from the UK, The ERG's clinical expert is of the opinion that the majority of the characteristics of the ARAMIS participants are representative of patients with nmCRPC who would be seen in clinical practice in the UK.

The methodological quality of the study was assessed by the company as being high on all assessment criteria taken from the University of York Centre for Reviews and Dissemination (CRD) guidance (Table 11, Section B.2.5, and Table 8, Appendix D.3, of the CS).[21] The ERG checked the risk of bias assessment of the ARAMIS trial presented in the CS against the original trial's publication and the CSR.[1, 20] The company's risk of bias assessment was considered to be appropriate.

The ARAMIS intervention groups well balanced for baseline characteristics including demographics, disease characteristics and prior therapies (Table 8, Section B.2.3 of the CS; reproduced as Table 7 below). Of the randomised participants, 12.2% were from North America (of whom [redacted]% were from the US), [redacted]% were from the Asia Pacific, and [redacted]% were from the rest of the world (of whom [redacted]% were from Europe). The median age of patients in ARAMIS was 74 years in both treatment arms, with most patients in the [redacted] and [redacted] age categories.

The majority of patients (83% and 71% for darolutamide + ADT and placebo + ADT, respectively) had no baseline regional pathological lymph nodes by central imaging review (Table 8, Section B.2.3 of the CS). However, during the efficacy review of all images including baseline images, performed by a separate group of independent central imaging reviewers, 5.2% (n=50) of patients in the darolutamide + ADT arm and 7.0% (n=39) of patients in the placebo + ADT arm were retrospectively confirmed to have metastases at randomisation.[20] These patients were included in the primary analysis of metastasis-free survival.

Table 7. Demographic and disease characteristics for the ARAMIS study population (reproduced from Table 8, Section B.2.3 of the CS)

	Darolutamide + ADT N=955	**Placebo + ADT N=554**
Age (yr); median (range)	74 (48-95)	74 (50-92)
Race (no., %)		
White	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
Missing [a]	[redacted]	[redacted]
Other	[redacted]	[redacted]
Geographic region (no., %)		
North America	108 (11)	76 (14)
Asia Pacific	119 (12)	67 (12)
Rest of the World (ROW) [b]	728 (76)	411 (74)
Median time from initial diagnosis (mo.) (range)	86.2 (2.6-337.5)	84.2 (0.5-344.7)
Presence of lymph nodes on central imaging review (no, %)		
Yes	163 (17)	158 (29)
No	792 (83)	396 (71)
Median serum PSA level (ng/ml) (range)	9.0 (0.3-858.3)	9.7 (1.5-885.2)
PSA doubling time		
Median (mo.) (range)	4.4 (0.7-11.0)	4.7 (0.7-13.2)
≤ 6 mo. (no., %)	667 (70)	371 (67)
> 6 mo. (no., %)	288 (30)	183 (33)
Median serum testosterone level (nmol/litre) (range) [c]	0.6 (0.2-25.9)	0.6 (0.2-7.3)
ECOG performance status (no., %)		
0	650 (68)	391 (71)
1	305 (32)	163 (29)
Gleason score at initial diagnosis		
Missing	[redacted]	[redacted]
<7	[redacted]	[redacted]
≥7	[redacted]	[redacted]
Use of bone-sparing agent (no., %)		
Yes	31 (3)	32 (6)
No	924 (97)	522 (94)
Previous hormonal therapy agents received (no., %) [d]		
One	177 (19)	103 (19)
Two or more	727 (76)	420 (76)
Not applicable [e]	51 (5)	31 (6)

ml=millilitres; mo.=months; ng=nanograms; no.=number; PSA=prostate-specific antigen; yr=year

At the time of data cut-off for the primary analysis (3rd September, 2018), the proportion of participants who discontinued study treatment was lower in the darolutamide+ADT arm (35.5%, 339/955) compared with the placebo+ADT arm (63.9%, 354/554) (Figure 2, Section D.2 of the CS). Of these, a lower percentage of participants discontinued treatment due to centrally confirmed metastasis in the darolutamide+ADT group than in the placebo+ADT group (112/955 [11.7%] and 129/554 [23.3%] for darolutamide+ADT and placebo+ADT, respectively), while a similar percentage of participants discontinued treatment due to adverse events in each treatment arm (86/955 [9.0%] and 47/554 [8.5%] for darolutamide+ADT and placebo+ADT, respectively) (Section D.2 of the CS).

Among those who discontinued study treatment (n = 339 and n = 354 for darolutamide+ADT and placebo+ADT, respectively), 100 participants in the darolutamide+ADT group and 130 participants in the placebo+ADT group received subsequent anti-cancer treatments for metastatic CRPC, with the most common treatments for darolutamide+ADT and placebo+ADT, respectively, being docetaxel (49% and 50.8%), enzalutamide (18% and 14.6%) and abiraterone (13% and 17.7%) (Table 15, Section B.2.6 of the CS). The proportion of study participants receiving anticancer therapy for metastatic CRPC after discontinuing study treatment is summarised in Table 8 below.

At the final data cut-off (15th November, 2019), [redacted]% ([redacted]/955) of the participants in the darolutamide+ADT group and [redacted]% ([redacted]/554) of the participants in the placebo+ADT group discontinued study treatment (Table 3, Appendix N of the CS). Among those who discontinued treatment (n = [redacted] for darolutamide+ADT and n= [redacted] for placebo+ADT), 170 participants in the darolutamide+ADT group and 167 participants in the placebo+ADT group received subsequent anti-cancer treatments for metastatic CRPC, with the most common treatments for darolutamide+ADT and placebo+ADT, respectively, being docetaxel ([redacted]% and [redacted]%), enzalutamide ([redacted]% and [redacted]%) and abiraterone ([redacted]% and [redacted]%) (Table 2 of the clarification response and Table 8 below).

The ERG clinical expert is of the opinion that the proportion of patients receiving subsequent treatments may not be truly reflective of the current practice in the UK. In particular, the proportion of patients receiving subsequent docetaxel appears relatively higher, and the proportion receiving subsequent enzalutamide and abiraterone appears relatively lower, than

would be expected in UK clinical practice. This is discussed further down in Chapter 3 and also in Chapter 4 of this report.

Table 8. Most common first subsequent anticancer therapy for metastatic CRPC in patients who discontinued study treatment (adapted from Table 15, Section B.2.6 of the CS; Table 2, Question A4 of the clarification response; Table 3, Section N5, Appendix N of the CS)

	Primary analysis (03 Sep 2018 data-cut)		Final analysis (15 Nov 2019 data-cut)	
	Darolutamide +ADT	**Placebo+ADT**	**Darolutamide +ADT**	**Placebo+ADT**
Randomised	955	554	955	554
Discontinued treatment	339/955 (35.5%)	354/554 (63.9%)	[redacted]/955 ([redacted]%)	[redacted]/554 ([redacted]%)
Due to centrally confirmed metastasis	112/955 (11.7%)	129/354 (23.3%)	NR	NR
Received subsequent therapy for mCRPC (cytotoxic chemothreapy and/or antineoplastic therapy)	100	130	170	167
Docetaxel	49/100 (49%)	66/130 (50.8%)	[redacted]/170 ([redacted]%)	[redacted]/167 ([redacted]%)
Enzalutamide	18/100 (18%)	19/130 (14.6%)	[redacted]/170 ([redacted]%)	[redacted]/167 ([redacted]%)
Abiraterone, abiraterone acetate	13/100 (13%)	23/130 (17.7%)	[redacted]/170 ([redacted]%)	[redacted]/167 ([redacted]%)

3.2.2 Primary and secondary efficacy endpoints

The primary efficacy endpoint in the ARAMIS study was metastasis-free survival. The study assessed the following secondary endpoints: overall survival, time to pain progression, time to initiation of first cytotoxic chemotherapy, time to first symptomatic skeletal event. The study also assessed the safety and adverse event profile of darolutamide along with a number of exploratory endpoints. The company provides a summary of the definitions for each outcome in Table 6, Document B, of the CS, which is reproduced as Table 9 below. The company states that the results of all efficacy and safety outcomes presented in the CS are based on the ARAMIS data cut-off of 3rd September 2018.

Table 9. Relevant endpoints and measures in ARAMIS (reproduced from Table 6, Document B of the CS)

Endpoint	Definition & timing of assessment / measure
Primary Efficacy Endpoint	
Metastasis-free survival (MFS)	Time from randomisation to confirmed evidence of metastasis or death from any cause, whichever occurred first. Deaths before documented metastasis and not later than 32 (+1) weeks after the last evaluable scan were included in this analysis. MFS was determined by the independent blinded central imaging review. Metastasis in bone was defined as appearance of 1 or more lesions that were confirmed by central imaging review, and metastasis in non-osseous tissue was defined as new distant pathologic lymph nodes or other pathological lesion according to RECIST 1.1.[22] New or progressive regional pathologic lymph nodes were not defined as metastasis. Death without prior documented metastasis and no later than two consecutive radiological assessment intervals after the last performed assessment was considered as an event. Patients not experiencing death or metastasis were censored at the last tumour assessment.
Secondary Endpoints	
Overall survival (OS)	Time from randomisation to death due to any cause. OS of patients not known to have died were censored at their last date of being known to be alive or at the database cut-off date, whichever came first.
Time to pain progression	Time from randomisation to pain progression, where progression was defined as an increase of 2 or more points from baseline in question 3 of the Brief Pain Inventory-Short Form questionnaire (BPI-SF) related to the worst pain in the last 24 hours taken as a 7-day average for post-baseline scores, or initiation of short or long-acting opioids for cancer pain, whichever came first. Initiation or change in the use of other non-opioid analgesics was not used in the analysis of pain progression.
Time to initiation of first cytotoxic chemotherapy	Time from randomisation to the start of the first cytotoxic chemotherapy cycle. Patients who had not taken cytotoxic chemotherapy were censored at their last visit. Cytotoxic chemotherapy was a specific antineoplastic therapy and was selected using ATC codes L01A, L01B, L01C, L01D, and L01X.
Time to first symptomatic skeletal event (SSE)	Time from randomisation to the occurrence of the first SSE. SSE was defined as external beam radiation therapy (EBRT) to relieve skeletal symptoms, new

Endpoint	Definition & timing of assessment / measure
	symptomatic pathologic bone fracture, occurrence of spinal cord compression, or tumour-related orthopaedic surgical intervention. Patients who did not reach the SSE were censored at their last visit (SSE assessment).
Exploratory endpoints	
Progression-free survival (PFS)	Time from randomisation to radiological disease progression based on independent blinded central imaging review, including progressing pelvic lymph nodes and new pathologic lymph nodes identified above or below the aortic bifurcation or death due to any cause, whichever occurred first. The radiological progression component of PFS was derived by taking all distant metastasis events as determined for the MFS endpoint, adding all local radiological progression events per RECIST 1.1 evaluation and choosing whatever came first in cases where both types of radiological progression were observed.
Time to first prostate cancer-related invasive procedures	Time from randomisation to the first prostate cancer-related invasive procedure. A prostate cancer related invasive procedure was defined as any procedure needed for alleviation of symptoms, signs or findings caused by progression of prostate cancer (e.g. catheterisation of the bladder, percutaneous drainage of hydronephrosis, palliative electro resection of the prostate, etc.).
Time to initiation of subsequent antineoplastic therapy	Time from randomisation to initiation of first antineoplastic therapy. Antineoplastic therapy (excluding cytotoxic chemotherapy) was selected using: • ATC code class L (antineoplastic and immunomodulating agents): L01 Antineoplastic agents (except cytotoxic chemotherapy L01A, L01B, L01C, L01D and L01X), L02 endocrine therapy and L03 immunostimulants. • ATC code class H: H02 Corticosteroids for systemic use.
Time from randomisation to first PSA progression	Defined in accordance with Prostate Cancer Working Group 2 (PCWG2) criteria.[23] PSA progression was defined as an increase of PSA of ≥25% and an absolute increase of PSA of ≥2 ng/mL above the nadir, which was confirmed by a consecutive value obtained 3 or more weeks later. PSA progression was only declared if observed at Week 16 or later after randomisation.
Percent of patients with PSA response	Defined according to PCWG2 criteria.[23] The percentage change of PSA from baseline was calculated and the proportion of patients achieving a decline of ≥50% from baseline was determined. PSA values were collected until the end-of-study treatment visit.
Percent of patients with ECOG performance status deterioration	ECOG PS criteria were used for measuring how the disease impacted the patients' daily living abilities during study treatment. These standard criteria include a scale of 0 (fully active, able to carry on all pre-diseases performance

Endpoint	Definition & timing of assessment / measure
	without restriction) to 4 (completely disabled; cannot carry on any self-care, totally confined to bed or chair). ECOG PS deterioration was defined as an increase to grade 3 or higher, with an increase of at least 2 from baseline.
Time to ECOG performance status deterioration	Time from randomisation to ECOG PS deterioration.
Time to opioid use for cancer pain	Time from randomisation to first opioid treatment for cancer pain. Opioid treatments were selected using ATC code starting with N02A.
Health Related Quality of Life (HRQoL):	PRO data as measured by the BPI-SF, FACT-P, the EQ-5D-3L, and EORTC-QLQ-PR25 described below.
BPI-SF	The BPI-SF questionnaire is a validated tool used to assess clinical pain related to cancer. Two scores can be derived: the pain severity score and the pain interference score. The BPI-SF assesses pain at its "worst", "least", "average", and "right now" (current pain), and the "pain severity" score is derived using the mean score of these 4 questions (questions 3 to 6 from the BPI-SF). The BPI-SF measures how much pain has interfered with seven daily activities, including general activity, walking ability, normal work, mood, enjoyment of life, relations with others, and sleep, and "pain interference" is scored as the mean of these 7 interference items. In the analyses, the rate of pain entered in questions 3 to 9 were used independently of the answer documented in question 1 (have you had pain other than these everyday kinds of pain today) of the BPI-SF.
FACT-P	The FACT-P questionnaire assesses prostate cancer-related quality of life and has been validated in the prostate cancer population. This questionnaire contains 5 domains (physical well-being, social/family well-being, emotional well-being, functional well-being, and additional concerns [also called prostate cancer subscale]). Each item can be answered on a 5-point (0–4) scale. The FACT-P total score is the sum of the scores of 39 items of the questionnaire and ranges from 1 to 156; the higher the score, the better the quality of life of prostate cancer patients.
Percent of patients with deterioration of FACT-P total score at 16 weeks	Patients were defined as having total QoL deterioration if they experienced a decrease of ≥10 points in FACT-P total score at 16 weeks compared with baseline.

Endpoint	Definition & timing of assessment / measure
Time to deterioration in PCS subscale score	According to the FACT-P scoring guide, all subscale items are summed to a total, which is the subscale score. QoL was also assessed using the prostate cancer-specific (PCS) subscale of the FACT-P questionnaire. Time from randomisation to deterioration in PCS subscale score. Patients were defined as having QoL deterioration if they experienced a change of ≥3 points in PCS compared with baseline.
EORTC-QLQ-PR25 **Percent of patients with improvement of EORTC-QLQ-PR25 urinary symptoms** **Time to worsening of EORTC-QLQ-PR25 urinary symptom score**	The EORTC-QLQ-PR25 questionnaire assesses prostate cancer-related QoL and has been validated in the prostate cancer population. The prostate cancer module is a 25-item questionnaire designed for use among patients with localised and metastatic prostate cancer. It includes subscales assessing urinary symptoms, bowel symptoms, hormonal treatment-related symptoms, incontinence aid, sexual activity, and sexual functioning. Patients were defined as having EORTC-QLQ-PR25 urinary improvement if they experienced a decrease of ≥8 points in the EORTC-QLQ-PR25 urinary symptoms score from baseline. Time from randomisation to deterioration. Patients were defined as having EORTC-QLQ-PR25 urinary symptoms deterioration if they experienced an increase of ≥8 points in EORTC-QLQ-PR25 urinary symptoms score from baseline.
EQ-5D-3L **Percent of patients with deterioration of EQ-5D-3L**	The EQ-5D-3L is a generic QoL preference-based instrument which has been validated in cancer populations to measure both utility and health status. Mobility, self-care, usual activities, pain/discomfort, and anxiety / depression are each assessed on 3-point categorical scales ranging from no problems to severe problems. Five health dimensions are summarised into a single score, the EQ-5D-3L index score. The EQ-5D-3L index score ranges -0.59 to 1, with higher scores representing better health states. The EQ-5D-3L also contains a visual analogue score (VAS) which records the patients' self-rated health status

Endpoint	Definition & timing of assessment / measure
utility index score at 16 weeks	on a vertical graduated visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). Patients were defined as having deterioration in the EQ-5D-3L index score if they experienced a deterioration of ≥0.06 points compared to baseline, at 16 weeks after start of treatment.
Other endpoints	
Safety	Adverse event (AE) assessment occurred at every visit including 30 days after last study treatment. AEs were classified by seriousness, intensity and causal relationship. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system (v21.0) and were graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Vital signs, physical examinations and Laboratory safety assessments (haematology, chemistry and urinalysis) were performed at every visit.
AE=adverse events; ATC=Anatomical Therapeutic Chemical; BPI-SF=Brief Pain Inventory-Short Form questionnaire; EBRT= external beam radiation therapy; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQ-PR25= European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Prostate Cancer Module; FACT-P=Functional Assessment of Cancer Therapy-Prostate; HRQoL=Health-related Quality of Life; MedDRA= Medical Dictionary for Regulatory Activities; MFS=metastasis-free survival; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; OS=overall survival; PCS=Prostate cancer-specific; PCWG2=Prostate Cancer Working Group 2; PFS=progression-free survival; PSA=prostate-specific antigen; RECIST=Response Evaluation Criteria in Solid Tumours; SSE=symptomatic skeletal event;	

Primary endpoint: Metastasis-free survival (MFS)

The company present the results of the ARAMIS MFS analysis in section B.2.6 of the CS. The primary MFS analysis was performed after 437 events occurred. The primary endpoint was reached with a median MFS of 40.4 months (95% CI lower limit 34.33, upper limit not reported) in the darolutamide + ADT arm, compared with 18.4 months (95% CI 15.5, 22.3) in the placebo + ADT arm (HR 0.41, 95% CI [0.34, 0.50], p<0.001). Event-free rates were superior for darolutamide + ADT compared with placebo + ADT at 4, 8, 12, 24 and 36 months. The company provides MFS event data and the Kaplan Meier analysis in Table 12 and Figure 5, Document B, of the CS.

[redacted]

[redacted] 18.6% (41/221) of the MFS events were deaths in the darolutamide + ADT arm compared with 8.8% (19/216) in the placebo + ADT arm. The company notes that, as part of the blinded central imaging review to determine metastases, all scans, including baseline scans, were reviewed. This was conducted by a different pool of radiologists to those that performed the study eligibility imaging review, resulting in 50/955 (5.2%) darolutamide patients and 39/554 (7.0%) placebo being re-classified as having metastases at baseline. These patients were included in the primary MFS analysis and counted as events at baseline. Censoring these patients produced results that were consistent with the primary analysis: median MFS of 40.51 months versus 22.08 months for the darolutamide + ADT and placebo + ADT arms respectively (HR 0.356, 95% CI [0.287, 0.441], p<0.000001).[2]

The company presents results of the MFS sensitivity analyses in Table 13, Document B, of the CS. All sensitivity analyses were consistent with the results of the primary analysis, with the exception of the non-stratified analysis. MFS subgroup analyses are presented in Appendix E of the CS. Darolutamide was favoured in all subgroups, [redacted].

Secondary endpoints

The company presents results of the ARAMIS secondary efficacy endpoints in section B.2.6 of the CS, including OS, time to pain progression, time to cytotoxic chemotherapy, and time to first symptomatic skeletal event. The secondary endpoints were tested with a hierarchical gatekeeping procedure with OS to be analysed first. Following the clarification stage of this submission, the company provided updated analyses using the data cut-off 15th November 2019 in Appendix N of the CS.

Overall survival (OS)

At the time of the company's primary OS analysis, darolutamide was associated with improved survival compared with placebo but this result did not reach the pre-specified alpha significance level of 0.0005 (HR 0.71 [95% CI 0.50, 0.99] p=0.045). The company presents subgroup analyses for OS in Appendix E of the CS.

[redacted]

A total of [redacted] events were recorded in the final OS analysis, using the 15th November 2019 data cut. The median OS had not been reached in either treatment arm. Based on a pre-specified alpha level of 0.0498, darolutamide plus androgen deprivation therapy (ADT) was shown to have a statistically significant increase in survival over ADT alone (HR [redacted], 95% CI [[redacted], [redacted]], p = [redacted]). A total of [redacted]% in the placebo arm had died, compared to [redacted]% in the darolutamide + ADT arm.[24] The company presents the final OS analysis data in Table 1, Appendix N, of the CS. Kaplan-Meier data and subgroup analyses data are also presented in Appendix N of the CS. Subgroup analyses were consistent with the main trial results. The ERG present the primary and final OS data in Table 10.

Table 10. Overall survival from the primary analysis (FAS; 03 September 2018 data-cut) and final analysis (FAS; 15th November 2019 data-cut) in the ARAMIS study (adapted from Table 14, Section B.2.6; and Table 1, Appendix N of the CS)

	Primary analysis (03 September 2018 data-cut)		**Final analysis (15 November 2019 data-cut)**	
	Darolutamide + ADT N=955	**Placebo+ ADT N=554**	**Darolutamide + ADT N=955**	**Placebo+ADT N=554**
Number (%) of patients with event	78 (8.2%)	58 (10.5%)	[redacted]	[redacted]
Number (%) of patients censored	877 (91.8%)	496 (89.5%)	[redacted]	[redacted]
OS (months)				
Median [95% CI]	Not yet reached	Not yet reached	[redacted]	[redacted]
Range (without censored values)	NA	NA	[redacted]	[redacted]
Range (including censored values)	NA	NA	[redacted]	[redacted]
HR: (Darolutamide/ Placebo) [95% CI] [a]	0.71 [0.50, 0.99]		[redacted]	
Two-sided p-value from log rank test	0.045		[redacted]	
CI=confidence interval; FAS=full analysis set; HR=hazard ratio;				

	Primary analysis (03 September 2018 data-cut)		Final analysis (15 November 2019 data-cut)	
	Darolutamide + ADT N=955	**Placebo+ ADT N=554**	**Darolutamide + ADT N=955**	**Placebo+ADT N=554**
A value cannot be estimated due to censored data ** censored observation [a] Hazard ratio <1 indicates superiority of darolutamide over placebo. Hazard ratio and its 95% CI was based on Cox Regression Model, stratified by PSADT (≤ 6 months vs. >6 months) and use of osteoclast-targeted therapy				

While the ERG agrees that the ARAMIS trial results appear to demonstrate an OS benefit for darolutamide, the ERG believes that this result should be interpreted cautiously as the proportions of patients receiving subsequent therapies, in the ARAMIS trial may not be generalisable to UK clinical practice. The company presents data for subsequent therapy in Table 15, Document B, of the CS and provided an updated analysis using the 15th November 2019 data cut, in Table 2 of their clarification response to the ERG, and this is reproduced by the ERG as Table 11 below. The update to the table used data recorded after the investigators were unblinded to treatment assignment whilst the data in table 15 of Document B was recorded during the double-blind part of the study when clinicians were not aware of treatment assignment.

While enzalutamide, abiraterone, docetaxel and cabazitaxel were the most used subsequent treatments in ARAMIS, it is the opinion of the ERG's clinical expert that fewer participants received subsequent abiraterone and enzalutamide treatments in ARAMIS compared to clinical practice and that the proportion of patients who received subsequent docetaxel in ARAMIS is higher than would be expected in clinical practice, and this may confound the OS results in favour of darolutamide. The ERG's clinical expert opinion is that darolutamide, which is a similar class of drug to enzalutamide, would be expected to provide a modest OS benefit in the context of the clinical pathway used in the NHS.

Table 12 below shows the information provided by the company in their Advisory Board Meeting Report (provided at clarification), which details the proportion of patients receiving first line subsequent treatments post progression, and that derived from the ARAMIS trial.

The first two lines of Table 12 show that according to the company's advisors the expected proportions of patients who received abiraterone, enzalutamde and docetaxel as subsequent treatments would be quite different depending on whether the patients had previously received darolutamide or ADT. Instead, in the ARAMIS trial, these proportions are broadly similar. The company's Advisory Board meeting report also indicates that enzalutamide would not be used post-progression for patients who had received darolutamide, while this was not the case in the ARAMIS trial.

Table 11. Subsequent use of cytotoxic chemotherapy and/or anti-neoplastic treatment in patients who discontinued study treatment (15th November 2019 data-cut) (reproduced from Table 2 of the clarification response)

Subsequent treatment number patients taking treatment, n (%)	**Darolutamide (n=170)**	**Placebo (n=167)**
Docetaxel	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]
Abiraterone, abiraterone acetate	[redacted]	[redacted]
Cabazitaxel, cabazitaxel acetone	[redacted]	[redacted]
Bicalutamide	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]
Estramustine, estramustine phosphate sodium	[redacted]	[redacted]
Flutamide	[redacted]	[redacted]
Apalutamide	[redacted]	[redacted]
Mitoxantrone	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]
Diethylstilbestrol	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]
Leuprorelin, leuprorelin acetate	[redacted]	[redacted]
Sipuleucel-t	[redacted]	[redacted]
Antineoplastic agents	[redacted]	[redacted]
Ethinylestradiol	[redacted]	[redacted]
Gemcitabine, gemcitabine hydrochloride	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
Cabozantinib	[redacted]	[redacted]
Capecitabine	[redacted]	[redacted]
Mitomycin	[redacted]	[redacted]
Pemetrexed	[redacted]	[redacted]
Vincristine	[redacted]	[redacted]
Darolutamide	[redacted]	[redacted]
Degarelix acetate	[redacted]	[redacted]

Subsequent treatment number patients taking treatment, n (%)	**Darolutamide (n=170)**	**Placebo (n=167)**
Docetaxel; prednisone	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]
Epirubicin hydrochloride	[redacted]	[redacted]
Etoposide	[redacted]	[redacted]
Fluorouracil	[redacted]	[redacted]
Goserelin acetate	[redacted]	[redacted]
Irinotecan hydrochloride	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]
Tegafur	[redacted]	[redacted]
Triptorelin acetate	[redacted]	[redacted]
Triptorelin embonate	[redacted]	[redacted]

Table 12. First line subsequent treatments post progression (Source: company's Advisory Board Meeting Report dated 4 Feb 2020)

		No treatment/ best supportive care	*ADT*	*Abiraterone acetate*	*Enzalutamide*	*Docetaxel*	*Radium-223 dichloride*	*Cabazitaxel*	*Bicalutamide*
Company's Advisory Board consensus	**Post Darolutamide**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Post ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinicians blinded to treatment assignment	**ARAMIS post Darolutamide**			[redacted]	[redacted]	[redacted]			[redacted]
	ARAMIS post ADT			[redacted]	[redacted]	[redacted]			[redacted]
Update which includes a spell when clinicians were aware of treatment assignment	**ARAMIS post Darolutamide**			[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
	ARAMIS post ADT			[redacted]	[redacted]	[redacted]		[redacted]	[redacted]

The company's advisors reached a consensus with regard to the proportion of subsequent treatments post progression on darolutamide and ADT (see Tables 1–2 of the Advisory Board meeting report).

- All the company's advisors suggested that enzalutamide or abiraterone are used only once in the treatment pathway.
- The company's advisors also explained that enzalutamide would not be prescribed post progression on darolutamide but that abiraterone may be beneficial post darolutamide in a small percentage of patients.
- The company's advisors were unsure whether they would be permitted by NHS guidance to prescribe abiraterone in the metastatic setting following treatment with darolutamide in the non-metastatic setting.
- For the purposes of determining subsequent therapies, it was assumed that abiraterone use would be permitted in the metastatic setting.

Other secondary endpoints

As of the cut-off date for the primary analysis (3rd September 2018), the results of the other secondary efficacy outcomes were consistent with those of OS and are in favour of darolutamide + ADT compared with placebo + ADT, including time to pain progression (HR 0.65, 95% CI [0.53, 0.79], p<0.001), and time to initiation of first cytotoxic chemotherapy (HR 0.43, 95% CI [0.31, 0.60], p <0.000001). As overall survival reached statistical significance in the company's updated analysis (15th November 2019 data-cut), the secondary efficacy outcomes were formally tested for significance and are reported by the company in Appendix N of the CS.

Exploratory endpoints

The company presents results of several exploratory endpoints for ARAMIS in section B.2.6 of the CS: progression-free survival, time to PSA progression, time to first prostate cancer-related invasive procedure, time to initiation of subsequent antineoplastic therapy, time to first opioid use for cancer pain, and time to ECOG deterioration. Analyses of the exploratory endpoints provides support for beneficial results for darolutamide + ADT compared with placebo + ADT. The company presents Kaplan-Meier estimates for PFS, time to PSA progression, and time to initiation of subsequent antineoplastic therapy in Figures 9, 10 and 11 respectively.

The company presents a summary of the results of the full analysis set of the ARAMIS study in Table 14 of the CS and this is reproduced (with amendment) by the ERG as Table 13.

Table 13. Summary of results from the ARAMIS study[1, 2] (FAS; 03 September 2018 data-cut unless otherwise stated) (adapted from Table 14, Section B.2.6; and Section N1 and N3, Appendix N of the CS)

Endpoint	Darolutamide N=955		Placebo N=554		Hazard Ratio [95% CI]	P Value
	Median duration (mo)	No. of events	Median duration (mo)	No. of events		
Primary endpoint						
Metastasis-free survival	40.4	221 (23.1%)	18.4	216 (39.0%)	0.41 [0.34-0.50]	<0.001
Secondary endpoints (03 September 2018 data-cut)						
Overall survival	NR	78 (8.2%)	NR	58 (10.5%)	0.71 [0.50-0.99]	0.045
Time to pain progression	40.3	251 (26.3%)	25.4	178 (32.1%)	0.65 [0.53-0.79]	<0.001
Time to cytotoxic chemotherapy	NR	73 (7.6%)	38.2	79 (14.3%)	0.43 [0.31-0.60]	<0.001
Time to first symptomatic skeletal event	NR	16 (1.7%)	NR	18 (3.2%)	0.43 [0.22-0.84]	0.01
Secondary endpoints (15 November 2019 data-cut)*						
Overall survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to cytotoxic chemotherapy	NR	NR	NR	NR	[redacted]	< [redacted]
Time-to-event Exploratory endpoints						
Progression-free survival	36.8	255 (26.7%)	14.8	258 (46.6%)	0.38 [0.32-0.45]	<0.001
Time to PSA progression	33.2	226 (23.7%)	7.3	368 (66.4%)	0.13 [].11-0.16)	<0.001
Time to first prostate cancer-related invasive procedure	NR	34 (3.6%)	NR	44 (7.9%)	0.39 [0.25-0.61]	<0.001
Time to initiation of subsequent anti-neoplastic therapy (excluding	NR	48 (5.0%)	NR	70 (12.6%)	0.33 [0.23-0.47]	<0.001

cytotoxic chemotherapy)						
Time to first opioid use for cancer pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to ECOG deterioration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; FAS=full analysis set; HR=hazard ratio; mo.=months; No.=number; PSA=prostate-specific antigen;

* For 'time to pain progression', the analysis performed using the cut-off date 3rd September 2018 is considered final; the median time to initiation of cytotoxic chemotherapy was [redacted]; the 'time to first symptomatic skeletal event' analysis using the cut-off date 18th November 2020 is not reported in Appendix N of the CS.

Time to treatment discontinuation

The company use time to treatment discontinuation as an endpoint in their economic model. The company state that the median treatment duration in ARAMIS was longer in the darolutamide arm (14.80 months) than the placebo arm (11.04 months). The company present results for the percentage of patients under treatment at different time categories: [redacted] ([redacted]% darolutamide versus [redacted]% placebo) >12 months to ≤30 months ([redacted]% darolutamide versus [redacted]% placebo) and >30 months ([redacted]% darolutamide versus [redacted]% placebo).[20]

Health-related quality of life

Health-related quality of life (HRQOL) was measured by FACT-P, EORTC-QLQ-PR25, EQ-5D-3L, and BPI-SF questionnaires in the ARAMIS study. The ERG considers these instruments adequate for measuring HRQOL in nmHRPC patients. Results indicate a statistically significant benefit for darolutamide in maintaining HRQOL compared with placebo for several dimensions of the HRQOL instruments, although the company state that clinically meaningful thresholds were not reached. EQ-5D-3L index and visual analogue scale results also favoured darolutamide but the company state that these results were not statistically significant or clinically meaningful. The company presents a summary of the HRQOL results in ARAMIS in Table 16, Document B, of the CS.

3.2.3 Adverse effects of treatment

The company presents safety data for darolutamide from the ARAMIS study in section B.2.10 of the CS. The safety population in ARAMIS comprised all patients who received at least one dose of study medication (n=954 darolutamide + ADT and n=554 placebo +ADT).

Median time on treatment was longer in the darolutamide arm than the placebo arm (14.8 versus 11.0 months) resulting in lower exposure in the placebo arm. To adjust for this, the company presents exposure-adjusted incidence rates for the ARAMIS adverse event (AE) data.

Overall, the incidence of treatment-emrgent adverse events (TEAEs) was similar between the darolutamide and placebo arms (83.2% versus 76.9%, respectively). Grade 1 or 2 TEAEs was comparable between treatment arms (54.6% versus 54.2% for darolutamide and placebo, respectively). Slightly more patients experienced grade 3 or 4 TEAEs in the darolutamide arm than in the placebo arm (24.7% versus 19.5%) and similar numbers experienced grade 5 TEAEs (3.9% versus 3.2%). Similar numbers of patients in both treatment arms experienced TEAEs leading to permanent discontinuation of study treatment (8.9% darolutamide versus 8.7% placebo). Most common reasons for discontinuation were cardiac failure (0.4% versu 0.7%) and death (0.4% versus 0.2%). Serious adverse events (SAEs) were also more commonly reported in the darolutamide arm than the placebo arm (24.8% versus 20% SAEs), although numbers of grade 3 and 4 drug-related SAEs were similar between treatment arms.

The company presents the most common TEAEs and exposure-adjusted TEAEs occurring in $\geq$2% of patients in Table 17, Document B, of the CS. Apart from fatigue (12.1% in the darolutamide +ADT arm versus 8.7% in the placebo arm) and pain in extremity (5.8% versus 3.2%), incidence of TEAEs was broadly similar in both treatment arms.

The company present the incidence of TEAEs that are known to occur with ADT or novel antiandrogens/second generation androgen-receptors in Table 18, Document B, of the CS and this is reproduced by the ERG as Table 14. Compared with placebo, darolutamide was not associated with a higher incidence of seizures, falls, fractures, mental impairment/cognitive disorders, depressed mood disorders, hypertension, cerebrovascular disorders. The company notes that darolutamide was associated with higher occurrence of rash (2.9% versu 0.9%) and higher rates of fatigue/asthenic conditions (15.8% versus 11.4%) compared with placebo. Cardiac disorders were also higher in the darolutamide arm (11.8%) than in the placebo arm (7.4%) of the ARAMIS trial. The company state that there were no clinically relevant effects on patient safety for any subgroup for either treatment arm.

Grade 5 TEAEs are presented in Table 19, Document B of the CS. Death occurred in 3.9% of patients treted with darolutamide and 3.2% of patients treated with placebo with one death in the the darolutamide arm and two deaths in the placebo arm considered TEAE-related deaths. The ERG agrees that the safety profile of darolutamide is in line with other second generation ARIs but is associated with less incidence of seizure.

Table 14. Incidence of TEAEs and exposure-adjusted TEAEs for special topics in the ARAMIS study (safety analysis set)[1, 20, 25]

Grouped TEAE term [a]	Darolutamide + ADT		Placebo		Incidence risk ratio for EAIR
	N=954 n (%)	EAIR per 100 PY[b]	N=554 n (%)	EAIR per 100 PY[b]	
Bone fracture [a]	40 (4.2)	3.0	20 (3.6)	3.5	0.85
Falls, including accident [a, c]	40 (4.2)	3.0	26 (4.7)	4.6	0.65
Fatigue / asthenic conditions [a]	151 (15.8)	11.3	63 (11.4)	11.1	1.02
Weight decreased	34 (3.6)	2.5	12 (2.2)	2.1	1.21
Seizures	2 (0.2)	0.1	1 (0.2)	0.2	0.85
Rash [a]	28 (2.9)	2.1	5 (0.9)	0.9	2.38
Dizziness including vertigo	43 (4.5)	3.2	22 (4.0)	3.9	0.83
Cardiac disorders (SOC)	113 (11.8)	N/A	41 (7.4)	N/A	N/A
Cardiac arrhythmias	64 (6.7)	4.7	22 (4.0)	3.8	1.24
Coronary artery disorders [a]	31 (3.2)	2.3	14 (2.5)	2.4	0.94
Heart failures [a]	18 (1.9)	1.3	5 (0.9)	0.9	1.53
CNS vascular disorders	16 (1.68)	1.2	10 (1.81)	1.7	0.68
Cerebral ischaemia [a]	13 (1.4)	1.0	8 (1.4)	1.4	0.69
Cerebral and intracranial haemorrhage	2 (0.21)	0.1	2 (0.36)	0.4	0.43
Hypertension	70 (7.34)	5.2	33 (5.96)	5.8	0.90
Vasodilation and flushing	54 (5.66)	4.0	23 (4.15)	4.1	1.00
Diabetes mellitus and hyperglycaemia	22 (2.31)	1.6	12 (2.17)	2.1	0.78
Mental impairment disorders [a]	16 (1.68)	1.2	10 (1.81)	1.7	0.68
Depressed mood disorders [a]	17 (1.78)	1.3	8 (1.44)	1.4	0.90
Breast disorders / gynaecomastia	22 (2.31)	1.6	9 (1.62)	1.6	1.04

CNS=central nervous system; EAIR=Exposure-adjusted incidence rate; MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients; n=number of patients with event; N/A=not available; PT=preferred term; PY=patient year; SAF=safety analysis set; SOC=system organ class; TEAE=treatment emergent adverse event;

[a] The specific terms used for MedDRA searches and reported PTs for grouped TEAE terms are as follows:

- Fatigue or asthenic conditions includes asthenic conditions, disturbances of consciousness, decreased strength and energy, malaise, lethargy, asthenia, and fatigue.

Grouped TEAE term [a]	Darolutamide + ADT		Placebo		Incidence risk ratio for EAIR
	N=954 n (%)	EAIR per 100 PY[b]	N=554 n (%)	EAIR per 100 PY[b]	
• Bone fracture includes any fractures and dislocations, limb fractures and dislocations, skull fractures, facial bone fractures and dislocations, spinal fractures and dislocations, thoracic cage fractures and dislocations, pelvic fractures and dislocations. • Rash includes dermatitis, erythema rash, macular rash, maculopapular rash, popular rash, pustular rash. • Coronary artery disorders include coronary artery disorders not elsewhere classified, coronary artery arteriosclerosis, coronary artery disease, coronary artery occlusion, coronary artery stenosis. • Heart failures includes heart failure not elsewhere classified, cardiac failure, acute cardiac failure, chronic cardiac failure, congestive cardiac failure, cardiogenic shock. • Cerebral ischaemia includes cerebral infarction, cerebral ischaemia, cerebrovascular accident, ischaemic stroke, transient ischaemic attack. • Diabetes mellitus and hyperglycaemia includes Hyperglycaemia, Diabetes mellitus, Diabetes mellitus inadequate control, Diabetic metabolic decompensation, Type 2 diabetes mellitus, Diabetic ketoacidosis • Mental impairment disorders include Alzheimer's disease, dementia, memory loss, mental impairment • Depressed mood disorders include depressive disorders, mood alterations with depressive symptoms. [b] EAIR of grouped events, defined as the number of patients with events divided by treatment duration in years. The rate is expressed in 100 patient years. [c] After review of the data, the search item for 'fall' was extended to include also the MedDRA PT 'accident'					

3.2.3.1 Supportive safety analyses

The company present information from a

[redacted] The ERG notes that these studies include patients from a different population to that considered relevant for this appraisal and they differ in terms of their dosing regimens; however, the ERG agrees with the company that they provide supportive evidence for the safety profile of darolutamide.

3.2.4 Meta-analyses

As evidence from only one RCT (ARAMIS study) was identified by the company as relevant to the decision problem of this appraisal, no meta-analyses were performed.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Indirect or multiple treatment comparisons were not conducted by the company for this appraisal.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

Indirect or multiple treatment comparisons were not conducted by the company for this appraisal.

3.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG requested for the time to event data for metastasis free survival, overall survival and time to initiation of subsequent antineoplastic therapy. However, the company informed the ERG that they do not have permission to share their patient level data (i.e. the time to event raw data underpinning the Kaplan Meier curves).

3.6 Conclusions of the clinical effectiveness section

After reviewing the analysis of the primary outcome presented in the CS, the ERG agrees with the company that there is a beneficial effect on metastasis free survival from darolutamide plus ADT compared with ADT alone. The summary statistics of event free rates and the Kaplan Meier plot consistently show a reduction in the risk of metastases at all time points. There is a large effect size on the primary outcome of metastases free survival in favour of darolutamide and ADT and the tight confidence interval around this effect size shows that the difference between the experimental arm and the control arm is significant.

The company provided an update on the secondary outcomes time to initiation of first cytotoxic chemotherapy and time on treatment at clarification. The analysis of time to pain progression and time on treatment which were presented in the company's main submission are considered to be the final analyses. The ERG has checked these analyses and is happy to accept the company's results related to the secondary endpoints. All the hazard ratios

indicate a longer duration for participants receiving darolutamide and therefore a benefit from darolutamide compare with placebo.

The company also provided the ERG with an updated result on overall survival. Although darolutamide plus ADT was shown to have a statistically significant increase in survival over ADT alone, the ERG has some concern with the small number of events considering the number of patients (254/1509, 16.8%). The company state that 240 overall survival events were planned for the analysis of overall survival and the median survival time is not reached in either treatment arm indicating the majority of survival times are censored. The Kaplan Meier curves for the overall survival and the summary statistics of survival rates (Appendix N of the CS) shows that a difference in survival probability between darolutamide and ADT appears to exist from 24 to 54 months. The ERG would question the size of the overall survival benefit being treated with darolutamide. The ERG is also concerned that the overall survival might be driven by the relatively low rate of participants progressing to subsequent treatments. Moreover, as stated earlier, the higher proportion of patients receiving subsequent docetaxel and lower proportion receiving enzalutamide and abiraterone may also be driving this difference. The proportion of subsequent treatments used in the ARAMIS trial are not those that the company have used in their economic model. The starting point for the extrapolation of the OS benefit would not have been reached under the assumed subsequent treatment proportions. The ERG agrees with the approach to use proportions suggested by the company's Advisory Board, which are more reflective of UK clinical practice and also agrees with the company's approach of fitting parametric survival curves separately for the intervention and control arms.

The company also submitted sub-group analysis of the overall survival endpoint.

[redacted]

The ERG has inspected the adverse events being reported in Tables 17-19 of the CS and noticed higher incidence of fatigue amongst patients receiving darolutamde and ADT. The

proportion of cardiac disorders is also higher amongst patients receiving darolutamide + ADT. The ERG is not concerned with any differences in serious adverse event or adverse event rates and in the ERG clinical expert's opinion, the type of frequency of adverse events observed in ARAMIS are reflective of those observed in UK clinical practice. The ERG agrees that the ARAMIS trial has not raised any new safety signals in the nmCRPC patient population.

4 COST EFFECTIVENESS

4.1 ERG comment on company's review of cost-effectiveness evidence

The company outlined the methods and results of their systematic literature review of cost-effectiveness studies in section B3.1 and appendix G of their submission. Their focus was on identifying full economic evaluations of any pharmacologic interventions in nmCRPC. Only English language reports were included, and searches were restricted to the past 10 years. The search strategies appear comprehensive and an appropriate range of databases were included. Efforts were also made to search relevant conference proceedings. The ERG has no issues with the methods applied.

The company identified 5 economic evaluations for inclusion in their review, which they summarized in Table 20 of their submission (CS, document B). Four of the studies related to appraisals of antiandrogens for nmCRPC by HTA agencies: 1) a Canadian Agency for Drugs and Technology in Health (CADTH) appraisal of enzalutamide; 2) a CADTH appraisal of apalutamide; 3) the NICE appraisal of enzalutamide (TA580); and 4) the US Institute for Clinical and Economic Review (ICER) report on antiandrogen therapies.[14, 27-29] A further published abstract reported on the cost-effectiveness of apalutamide in a US setting.[30]

The company did not draw conclusions regarding the cost-effectiveness of the identified technologies but considered the model structures. All used a nmCRPC and a mCRPC health state, and either a Markov model, partitioned survival analysis (Part-SA) model, or a hybrid of these approaches. A theoretical benefit of the Markov approach in this context is that it can capture the expected transitions through subsequent lines of therapy available to patients once they progress to mCRPC, while accounting for an increasing risk of mortality with progression. Part-SA models which rely on a single OS curve can only provide the state distribution at any given point in time, and do not explicitly capture the proportion of a cohort making transitions from one state to another. Therefore, whilst such models are less data intensive and transparent with respect to projections of progression-free survival and OS, they do require assumptions to account for expected transitions through subsequent treatments and the costs and QALYs associated with this.

It is worth noting that the previous NICE appraisal of enzalutamide for nmCRPC used a semi-Markov approach, whereby the mortality risk was split by progression status (nmCPRC/mCRPC), allowing expected transitions to mCRPC and subsequent lines of treatment (PD1-PD3) to be captured.[14] However, the mortality rate remained equal across subsequent lines of therapy at any given time point, resulting in remaining uncertainty around transitions through and time spent in different lines of subsequent therapy. In addition, the committee for TA580 felt that the splitting of immature OS data by progression status introduced further uncertainty around the modelled OS projections, which outweighed the benefits of the more complex structure. This has had some bearing on the approach taken by the company in the current submission for darolutamide.

4.2 Summary and critique of the company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 15. NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes, patients only.
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	A systematic review of was conducted, but all the relevant evidence for efficacy came from a single trial.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-	Yes, QALYs based on EQ-5D values were calculated.

	5D is the preferred measure of health-related quality of life in adults.	
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes, EQ-5D status reported by patients. Given limited available of utility data for the mCRPC state in the ARAMIS trial, values for this state were sourced from other trials in the relevant population.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	All health state values reflect UK population preferences based on the EQ-5D 3L general population tariff.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Included as appropriate, although some uncertainty relating to the small sample of patients used to inform resource use elements.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes, a discount rate of 3.5% appropriately applied.
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

The company developed a three-state, partitioned survival, cost-effectiveness model comparing treatment with darolutamide plus ADT with ADT alone in high-risk patients with nmCRPC.

The model consists of three health states commonly used in oncology modelling: nmCRPC (non-metastatic progression-free), mCRPC (metastatic progressed) and dead. Patients enter the model in the nmCPRC health state where they are at risk of metastatic progression or death (Figure 12, Document B of the CS).

In the darolutamide arm in the nmCRPC health state, ToT data are used to model patients on active treatment (darolutamide plus ADT) and no active treatment (ADT

alone). Patients discontinue darolutamide treatment upon metastatic progression as per the SmPC. The mCRPC health state captures patients receiving first-, second- and third-line treatments and best supportive care. Metastatic progression is included as a single health state in the model but the costs associated with each line of treatment are estimated separately and a single weighted-average utility value is applied to both arms based on the expected distribution of time spent on each line of treatment. The post-progression treatment pathways applied in each arm of the model were derived from clinical expert opinion, rather than the proportions observed in the ARAMIS trial, to better reflect current UK NHS practice.

The company acknowledged that the three-state model structure may oversimplify the mCRPC health state. As patients can receive up to three lines of therapy and experience a range of outcomes, the use of a single health state results in a degree of uncertainty. The company justified the approach used as it avoids splitting the progressed state into separate lines of treatment which would require the use of data from external trials thereby increasing uncertainty. While the three-state partitioned survival model is generally appropriate for modelling oncology treatments, a more granular structure may be more appropriate given the post-progression treatment sequence is quite different for each arm of the model. Most patients in the ADT arm will receive abiraterone or enzalutamide as first-line treatment post-progression whereas most patients who progress following darolutamide will receive docetaxel. However, the company note the conclusion reached by the committee in the recent TA580 where a more complicated model structure was deemed to have unnecessarily introduced additional uncertainty. Given this, the ERG considers the standard three-state model structure adequately captures the nature of the disease but note there are several limitations with respect to accurately capturing the expected costs and QALYs accruing in the mCRPC health state.

4.2.3 Population

The population reflects patients in the ARAMIS trial: adult men with nmCRPC who are at high risk of developing metastatic disease. High risk is defined as having a baseline PSA level ≥ 2ng/ml and a PSA doubling time (PSADT) of ≤ 10 months. However, the definition of high risk in ARAMIS may not reflect what is considered high risk in clinical practice where a PSA doubling time of < 6 months may be used.

This issue was also considered in TA580 and while it was acknowledged this was an area of uncertainty the committee concluded it was unlikely to affect the generalisability of the results. A further point recorded in the FAD for TA580 is that the nmCRPC population is a small group of patients, which is becoming smaller due to use of more sensitive radiographic imaging. The ERG note that nmCRPC patients in the ARAMIS trial were identified by conventional imaging techniques (computed tomography, magnetic resonance imaging, and bone scan).

4.2.4 Interventions and comparators

Intervention

Darolutamide is included in the model at a dose of 600mg (two 300mg tablets) twice daily until metastatic disease progression or unacceptable toxicity. ADT is included as background therapy throughout.

Comparator

The comparator is ADT alone as there are no other active treatments recommended for use in nmCRPC in the UK. The use of ADT as the comparator is consistent with the NICE scope, TA580 and the comparator in the ARAMIS trial. ADT consisted of common ADT treatments in line with the ARAMIS trial (40% leuporelin, 30% goserelin, 20% triptorelin and 10% buserelin). Patients in both arms receive ADT for the model time horizon. Following progression, patients can receive up to three lines of subsequent treatment plus best supportive care. The subsequent treatments and proportions observed in the ARAMIS trial did not reflect the NHS treatment pathway in practice so instead the model included estimates from the company's advisory board (see Figure 3 and Table 42 of company submission). In the darolutamide arm, of the patients estimated to transition to the mCRPC state, 60% receive docetaxel as first line therapy (mCRPC1) while 85% of patients in the ADT arm receive either enzalutamide (42.5%) or abiraterone (42.5%) at this treatment line. The ERG consider the types and proportions of subsequent treatments included in the model to be broadly reflective of NHS practice.

4.2.5 Perspective, time horizon and discounting

The model uses a 28-day cycle length and a lifetime horizon of 27 years. A discount rate of 3.5% is applied to costs and QALYs as per NICE guidance. By 27 years, any

remaining survivors would be 100 years old based on mean age of 73.62 at model entry. Less than 1% of the cohort remain alive beyond [redacted] years and [redacted] years in the ADT and darolutamide plus ADT arms of the model, respectively.

4.2.6 Treatment effectiveness and extrapolation

Overall survival

The November 2019 data cut from ARAMIS provided OS data out to a maximum of about 5 years, but with heavy censoring in the tails of the KM curves. Median OS had not been reached in either treatment arm. Kaplan Maier data were presented with and without adjustment for crossover from ADT to darolutamide, with the adjustments having a small downward impact on the KM curves for ADT. The company followed DSU guidance and rejected the proportional hazard assumption in favour of independently fitted curves. They fitted six standard parametric curves to the observed KM data in each arm (see Appendix N of the company submission, Figures 19-21). Curves were fitted to the unadjusted and the adjusted KM data, with the unadjusted curves applied in the company base case (reproduced as Figure 2 below) and the adjusted curves explored in scenario analysis. The projected OS estimates for each curve at selected time points were provided by the company in response to the clarification letter (reproduced in Table 16 below). Considering AIC/BIC (CS, Appendix N, Table 4) visual fit, and clinical expert opinion, the company selected the Weibull curve for both the darolutamide plus ADT and ADT arms of the model. The ERG agrees that these provide the lowest AIC and BIC overall, and provide a reasonable visual fit to the observed data.

The ERG notes the relative immaturity of the OS data, and the corresponding wide variation in the projections provided by the alternative curves beyond the observed follow-up period. The Weibull provides the second most pessimistic projection of 10-year survival for ADT, and the third most pessimistic projection for darolutamide. There are no long-term data available by which to externally validate the OS projections for the high risk nmCRPC population. Four-year overall survival in the placebo arm of the SPARTAN trial, at approximately 65%, is a little higher than corresponding OS in the placebo arm of the ARAMIS trial ([redacted]). The ERGs clinical advisor believed that the Weibull provided a reasonable extrapolation for the ADT arm based on clinical experience. However, he believed the Weibull was optimistic

for darolutamide, and expected OS for the darolutamide arm of the trial to fall somewhere between the generalised gamma and Weibull curves (Figure 2). This assertion was because, although no metastases are yet visible on imaging, the population has already developed castrate resistant prostate cancer. With this significant milestone reached, the ERG's clinical advisor was sceptical about the probability of anyone surviving to 20 years.

Figure 2. Parametric survival analysis on the unadjusted OS Kaplan-Meier data from 15th November 2019 ARAMIS data-cut (source: Figure 19, Company submission, Appendix N)

Table 16. Survival analysis estimates OS 15 NOV 2019 data-cut (unadjusted for cross-over) (Source: Table 5, Company response to the clarification letter)

Parametric model	**Predicted survival**				
	5 years	**10 years**	**15 years**	**20 years**	**25 years**
Darolutamide + ADT arm					
Exponential	73.5%	54.0%	39.5%	29.0%	21.3%
Generalised gamma	63.3%	7.4%	0.0%	0.0%	0.0%
Gompertz	59.4%	0.7%	0.0%	0.0%	0.0%
Log-logistic	67.2%	39.4%	24.8%	17.0%	12.4%
Log-normal	71.0%	50.8%	38.4%	30.3%	24.6%

Weibull	**65.5%**	**28.3%**	**9.0%**	**2.3%**	**0.5%**
ADT arm					
Exponential	65.1%	42.4%	27.4%	17.9%	11.6%
Generalised gamma	52.5%	16.9%	4.6%	1.2%	0.3%
Gompertz	42.7%	0.0%	0.0%	0.0%	0.0%
Log-logistic	53.1%	22.6%	11.6%	7.0%	4.6%
Log-normal	57.7%	31.4%	18.8%	12.2%	8.3%
Weibull	**49.8%**	**8.8%**	**0.6%**	**0.0%**	**0.0%**

Darolutamide is the first second generation NSAA to demonstrate a significant effect on overall survival compared to ADT alone in the nmCRPC setting. The recently published second interim analysis of the SPARTAN trial indicates a trend towards improved OS with apalutamide versus placebo, but not significant at the pre-specified adjusted significance level of 0.0121 (p=0.0197).[31] More recently it has been announced that the final OS analysis of the PROSPER trial has demonstrated a significant survival benefit for enzalutamide plus ADT versus placebo plus ADT in men with high risk nmCRPC (https://newsroom.astellas.us/2020-02-11-XTANDI-R-enzalutamide-Demonstrates-Significant-Improvement-in-Overall-Survival-in-Phase-3-PROSPER-Trial-of-Patients-with-nmCRPC). However, the data are not yet published and available for scrutiny. The above generally supports the OS gain seen in the ARAMIS trial. However, as discussed in the clinical effectiveness section, a question does remain over the generalisability of this finding to the NHS treatment pathway.

This relates primarily to discordance between the observed use of subsequent treatments in the ARAMIS trial and the expected use of subsequent treatments in the NHS. Data from the November 2019 cut of ARAMIS suggest that 35% (=170/490) and 41% (=167/407) of those who had discontinued study treatment had moved onto a subsequent treatment in the darolutamide and placebo arms, respectively. This seems low in comparison with clinical expectation outlined in Figure 3 of the CS. Further, the company acknowledged that the proportional distribution of first subsequent treatments in ARAMIS were not in keeping with the NHS proportions suggested by

clinical experts, particularly in relation to the use of abiraterone and enzalutamide (Table 17). A number of patients had also received abiraterone and enzalutamide in subsequent lines of treatment, as suggested by the data presented in Table 2 of the company response to the clarification letter, but use of these drugs remains high in the darolutamide arm, and low in the ADT arm of the ARAMIS trial compared to NHS practice. Thus, the ERG questions the generalisability of the OS benefit observed in the ARAMIS trial to UK clinical practice where patients with nmCRPC are monitored closely and generally treated with enzalutamide or abiraterone when metastases are detected.

The company acknowledged the discrepancy between subsequent treatments observed in the ARAMIS trial and those expected in UK clinical practice in their response to the clarification letter. They noted that the discrepancy reflects the blinded nature of the ARAMIS trial, where subsequent treatments were assigned without knowledge of study drug up until the data cut-off for the primary analysis (3rd September, 2018).

To further address this uncertainty, the company provided a post hoc analysis in response to the clarification letter, showing Kaplan Maier plots of survival from the point of initiating subsequent treatment in the darolutamide plus ADT and ADT (placebo) arms of ARAMIS.

[redacted]The company highlight the limitations of these analyses, including the small numbers of patients and the breaking of randomisation. Further, the ERG understands that the subsequent treatment groups in this analysis included patients who had received each of the subsequent treatments at any line (not just first line following progression), and so the groups may not be mutually exclusive. Therefore, the KM curves in Figures 5 and 6 of the company responses do not necessarily reflect the subsequent treatment pathways used in the NHS and assumed in the model.

Considering the above discussions, the ERG has concerns that the ARAMIS trial may overestimate the OS benefit that would be seen if darolutamide were adopted within

the UK NHS clinical treatment pathway. However, the magnitude of any bias is uncertain, and the ERG acknowledge the company's point that there is no easy way to deal with these uncertainties in the analysis of OS data. The ERG therefore believe that the best approach is to run scenarios that reduce the relative OS benefit from future time points, either shifting the ADT OS curve upwards (reflecting greater access to effective treatment), or shifting the darolutamide OS curve downward. The company have provided such analyses, which are helpful for exploring the uncertainty.

Table 17 Proportion of patients who received abiraterone, enzalutamide and docetaxel in the ARAMIS trial data cut 3 September 2018, 15 November 2019 and the proportion expected in UK clinical practice (Source, Table 17, company response to the clarification letter)

Subsequent treatment	**Percentage of patients receiving the subsequent treatment at the 3 September 2018 data cut**		**Percentage of patients receiving the subsequent treatment at the 15 November 2019 data cut**		**Percentage of patients receiving the treatment in UK clinical practice[32]**	
	Darolutamide + ADT	**ADT**	**Darolutamide + ADT**	**ADT**	**Darolutamide + ADT**	**ADT**
Abiraterone	13%	18%	[redacted]	[redacted]	2.5%	42.5%
Enzalutamide	18%	15%	[redacted]	[redacted]	0%	42.5%
Docetaxel	49%	51%	[redacted]	[redacted]	60%	10%
Key: ADT; androgen deprivation therapy						

Key: OS, overall survival.

Figure 3. Kaplan-Meier plot of overall survival of the ADT arm split by the subsequent treatments abiraterone, enzalutamide and docetaxel from the start of subsequent treatment to the data cut off (15 November 2019) (Source: Figure 6, Company response to the clarification letter)

Metastasis free survival (MFS)

The company uses parametric curves fitted to MFS data from ARAMIS to partition the cohort between the nmCRPC and mCRPC health states in the model. The MFS data are relatively mature, particularly in the ADT arm. Based on AIC/BIC visual fit and clinical expert opinion, the company selected independently fitted Weibull curves for each arm of the model. Alternative extrapolations also caused extrapolated MFS to be higher than OS at future time points, which would require adjustment in the model. The ERG's clinical expert broadly agreed with this selection based on the September 2018 data cut. The fitted curves are shown in Figures 20 to 22, Document B of the CS. The corresponding estimated proportions at selected time points were provided by the company at clarification (reproduced below as Table 18). However, the ERG have concerns that the company have not updated the MFS curves to the Nov 2019 data cut, as they did for OS and ToT (implications discussed below)

Table 18. Survival analysis estimates MFS-BMC 03 SEP 2018 data-cut (Source: Table 3, company response to the clarification letter).

Parametric model	Predicted survival				
	5 years	10 years	15 years	20 years	25 years
Darolutamide + ADT arm					
Exponential	49.3%	24.3%	11.8%	5.8%	2.9%
Generalised gamma	43.9%	22.2%	12.8%	8.1%	5.4%
Gompertz	21.8%	0.0%	0.0%	0.0%	0.0%
Log-logistic	39.7%	18.2%	10.5%	7.0%	5.0%
Log-normal	45.6%	25.1%	15.8%	10.9%	7.9%
Weibull	**32.2%**	**4.7%**	**0.4%**	**0.0%**	**0.0%**
ADT arm					
Exponential	16.2%	2.6%	0.4%	0.1%	0.0%
Generalised gamma	23.8%	13.6%	9.6%	7.5%	6.2%
Gompertz	2.3%	0.0%	0.0%	0.0%	0.0%
Log-logistic	13.8%	4.8%	2.5%	1.6%	1.1%
Log-normal	14.6%	4.2%	1.7%	0.8%	0.5%
Weibull	**4.8%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**

Time on treatment (ToT)

The company also used parametric curves fitted to the ToT data from the darolutamide arm of the ARAMIS trial to divide the cohort in nmCRPC state between those on-treatment and those off-treatment. The curving fitting followed the same approach as per OS and MFS and considered the same candidate distributions. As per OS, the curve fitting was updated at the clarification stage to accommodate the more recent November 2019 data cut. (See Appendix N of the CS, Figure 22 for details). The increased duration of follow-up available had caused the KM curves for ToT to fall below the previous estimates based on the September 2018 data cut (see Appendix N of the CS, Figure 6), and subsequently the parametric curves were all lower than the corresponding curves fitted to the September 2018 dataset.

[redacted]

[redacted] and based on the clinical expert feedback obtained by the company, the higher Weibull curve was discussed as an alternative (Table 19). With the revised analysis, the [redacted] resulting in substantially reduced darolutamide treatment costs in the nmCRPC state, and a corresponding reduction in the ICER. The selected ToT curve is an important parameter in the model.

Based on the ERGs clinical expert's advice, the ToT curve can be expected to track quite closely to the MFS curve in clinical practice, as few patients would be expected to discontinue whilst on treatment and responding. The ERG has concerns about the decision to update the ToT curve for the latter data cut whilst maintaining the original September 2018 curve for MFS. The result of this has been a greater divergence between ToT and MFS (Figure 4), and it is unclear whether the MFS would have similarly dropped with the use of more mature data. This mismatch between the datasets used for the two curves adds uncertainty to the model. The ERG, therefore, believes that exploratory scenarios using lower MFS extrapolations, and/or higher ToT curves from both the Sept 2018 and the November 2019 analysis, are warranted.

Table 19. Survival analysis estimates TOT 03 SEP 2018 data-cut (Source: Table 8 of the company response to the clarification letter)

Parametric model	**Predicted survival**				
	5 years	**10 years**	**15 years**	**20 years**	**25 years**
Darolutamide + ADT arm					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 20. Survival analysis estimates TOT 15 NOV 2019 data-cut (Source: Table 8 of the company response to the clarification letter)

Parametric model	Predicted survival				
	5 years	10 years	15 years	20 years	25 years
Darolutamide + ADT arm					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 4. Darolutamide MFS and ToT curves

Face validity of the state occupancy predicted by the combined curve selections

In their response to the clarification letter, the company provided a breakdown of the expected life years spent in mCRPC subsequent treatment lines when using their preferred set of curves. The figures are reproduced in Table 21 below and indicate that patients in the darolutamide arm of the model accumulate more undiscounted life

years in the mCRPC state than patients in the ADT arm. This seems somewhat counterintuitive to the ERG, as patients in the ADT arm will progress more quickly to the mCPRC state where they have greater access to more effective treatments for mCRPC than patients who progress on darolutmatide. Thus, it may be expected that patients in the ADT arm would accumulate greater life years in these states compared to patients in the darolutamide arm.

Table 21. Mean LYs by mCRPC sub-states (Source, Table 21 of the company response to the clarification letter)

Outcome	Darolutamide + ADT Lys	ADT Lys
mCRPC 1	[redacted]	[redacted]
mCRPC 2	[redacted]	[redacted]
mCRPC 3	[redacted]	[redacted]
BSC	[redacted]	[redacted]
Total	[redacted]	[redacted]

This effect may suggest either an overprediction of long-term survival in the darolutamide arm, underprediction of long-term OS in the ADT arm, overprediction of MFS in the ADT arm, or underprediction of MFS in the darolutamide arm, or a combination of the above. Given the relative maturity of the MFS data, the ERG believes it more likely that the inconsistency is caused by the selection of OS curves, and most probably an overoptimistic projection of OS for darolutamide. Assessing the proportional reduction in the hazard of mortality for darolutamide across the model time horizon, [redacted] (Figure 5). This long-term relative treatment efficacy, combined with the predicted increase in mCRPC life years for darolutamide versus ADT, appears questionable given the fewer treatment options available to patients following progression on darolutamide.

[redacted]

Figure 5. Relative hazard of mortality over time in the model

4.2.7 Health related quality of life

Health-related quality of life is captured in the model by applying utility weights to each health state and utility decrements for adverse events. A baseline utility is applied to the nmCRPC health state with a lower utility upon progression to mCRPC. The progressed utility value is a weighted average of four separate utilities capturing declining quality of life over time as patients move through up to three treatment lines post-progression (plus best supportive care). Utility decrements were applied for grade 3 or 4 AEs occurring in ≥5% of patients. SSEs were also included regardless of grade or frequency. See table 30 of CS for AEs and SSE rates.

Utility weights: nmCRPC and mCRPC health states

For the nmCRPC health state, the utility weight was estimated using EQ-5D-3L data collected in the ARAMIS trial. For the mCRPC health state utility values were sourced from TA580, where they were originally based on EQ-5D data from the PROSPER, AFFIRM and PREVAIL trials.[14, 33-35] In ARAMIS, EQ-5D data were collected at screening, visit 1, visit 4 (16 weeks ± 7 days) and at the end of the study treatment visit. Univariate mixed-effects models were fitted to the utility data and identified age and health state as statistically significant covariates. As treatment arm

was not shown to be a significant covariate, the nmCRPC utility value was estimated using the pooled BMC mixed-effects model where data from both treatment arms were pooled together. The base case value for the nmCRPC health state in the model is 0.813.

Due to the limited EQ-5D data collected for patients who had confirmed metastases, the company did not use the ARAMIS trial data to estimate the mCRPC utility value. Instead, a weighted average utility value was estimated based on the expected time spent on each line of treatment in the mCRPC health state (mCRPC1, mCRPC2, mCRPC3 and BSC) using mean life year estimates from TA377[36] as estimates from TA580 were not published. The utility values used to estimate the weighted average for the mCRPC health state were taken from EQ-5D data collected in several external trials: PROSPER (mCRPC1 and mCRPC2), AFFIRM (mCRPC3) and PREVAIL (BSC).[33-35] This approach resulted in a weighted average utility value of 0.704 which was applied to both arms.

The ERG was concerned that applying the same utility value in each arm for the mCRPC health state could introduce some bias in the model. In addition, the life year estimates from TA377 used to estimate the weighted average utility value were based on patients receiving BSC which may underestimate the time on post-progression treatments, particularly for the ADT alone arm.[36] As described previously, the post-progression treatment pathways are quite different in each arm of the model as most patients in the ADT arm receive enzalutamide or abiraterone first-line post-progression, whereas most patients in the darolutamide arm receive docetaxel. As patients in the ADT arm are receiving more effective treatments post-progression, they will spend a larger proportion of time in the mCRPC1 state with associated higher quality of life than patients who progress on darolutamide. This was confirmed in response to a clarification question where the company acknowledged the limitations with the approach used to estimate the nmCRPC utility value, and provided an alternative treatment arm specific approach, which they included in their revised base case. This involved estimating the weighted average utility value separately for the darolutamide and ADT arms, taking account of the proportion of patients receiving enzalutamide or abiraterone in mCRPC1. Using this approach, a higher weighted average progressed utility value was estimated for the ADT arm of

the model compared to the darolutamide plus ADT arm (0.743 versus 0.705), resulting in a small increase in the ICER.

Sensitivity analysis was also provided using alternative mCRPC utility values from TA580 (first assessment after progression = 0.810) and TA412 (0.620).[14, 37] EQ-5D data were collected in patients with mCRPC in ARAMIS, and the company regression estimated that utility declined by 0.064 upon progression. However, the impact of using these data was not explored in the sensitivity analysis. The ERG notes that in TA580 the committee expressed a preference for using EQ-5D data collected in the key trial to inform the utility value for the first progressed disease state to retain consistency with the clinical data source. In response to a clarification question the company emphasised the lack of EQ-5D data available from ARAMIS to allow a robust utility estimate for the mCRPC health state as only 6% of data were from patients with confirmed metastases. The mean time between confirmed metastasis and EQ-5D response was [redacted] days in the darolutamide arm and [redacted] days in the ADT arm suggesting the data represent the quality of life of patients relatively early in the progressed health state. The ERG agree using the ARAMIS trial data would be uncertain and also note that the company's base case and revised utility estimate for the mCRPC health state could be considered conservative relative to the ARAMIS data as the decrement from nmCRPC to mCRPC1 is smaller. In summary, while there remain uncertainties associated with the derivation of the progressed utility value in the model, the ERG is satisfied that the revised base case approach to utility values in the mCRPC health state is broadly appropriate.

Utility decrements: AEs and SSEs

The impact of AEs and SSEs on quality of life is included separately by applying utility decrements sourced from a number of published studies combined with the rates from ARAMIS. Once off adverse event probabilities were taken as the percentage of patients experiencing each of them over the ARAMIS follow-up period as reported by Fizazi et al (2019).[1] This approach may tend to underestimate the impact, as it ignores the possibility of events recurring in patients. Further, the approach of focussing on the frequency of Grade3/4 AEs that had an occurrence of any severity ≥ 5%, may underplay their potential impact. The sum of Grade 3/4 AE probabilities included in the company model comes to 0.075 and 0.069 in the

darolutamide and ADT arms, respectively. The reported percentages of patients experiencing a Grade 3/4 AE reported by Fizazi were 24.7% and 19.5%, respectively. The durations of AEs and SSEs were taken from TA580 and TA377.[14, 36] Based on these data, a one-off QALY decrement is applied in the model in the first cycle. See Table 31 of the company submission for details of the individual utility decrements and Table 32 for the QALY decrements by treatment arm.

The utility decrements are taken from a range of studies and populations but no discussion was provided on the comparability of these data sources with the patient population who would be eligible for darolutamide. There is some uncertainty in the derivation of the one-off QALY decrement due to the range of sources and assumptions used. However, this is not a key driver of the model and most of the values have been used in previous relevant appraisals (TA580 and TA377).[14, 36]

4.2.8 Resources and costs

The CS presents the cost of treatment of CRPC patients to comprise of the following components:

- Drug acquisition and administration costs
- Monitoring costs
- Costs associated with the management of AEs and SSEs
- Subsequent treatment costs
- End-of-life care costs

Drug and administration cost in the nmCRPC state

Drug costs of darolutamide were applied to the proportion of patients on treatment in the nmCRPC state. The treatment duration of darolutamide was determined by the extrapolation of the ToT curve from the ARAMIS trial. As discussed in section 4.2.6, the ERG has concerns about the company's pairing of the updated ToT curve, based on the November 2019 data cut, with the MFS curve based on the September 2018 data cut of ARAMIS (Figure 3 above). The resulting increased divergence of the curves may underestimate the treatment cost to benefit ratio in the nmCRPC health state.

The cost of ADT was applied to all patients in the nmCRPC state in both arms of the model, and for the entire time horizon of the model, an assumption that has been validated by clinical experts, including the ERGs own clinical expert. Table 35 of the company submission provides a summary of the drug costs applied for darolutamide and ADT in the model. A proposed simple patient access scheme was applied to the acquisition costs for darolutamide.

Drug administration costs are shown in Table 37 of the company submission. The ERG noted in the clarification letter to the company that their application of PSSRU costs, based on an hour of staff time, may be inappropriate for use per administration of ADT. In their response to the clarification letter the company adjusted this in a scenario where they used the administration costs from TA404 inflated to 2019 prices; this resulted in only a very small decrease in the ICER (See Table 19 of the company's response to the clarification letter).

Drug and administration cost of the mCRPC state

The drug and administration costs for subsequent lines of treatment were applied as a one-off cost to those progressing to mCRPC, based on the assumed distribution of subsequent treatments and their expected durations, and the extrapolated OS and MFS curves.

The distribution of subsequent treatments applied to the mCRPC state were sourced from the company's Advisory Board in the company base case, which the ERG's clinical expert agrees are generally representative of the current NHS treatment pathway (Table 22). As mentioned in section 4.2.6, patients who progress on darolutamide have less access to the more effective life extending treatments (enzalutamide or abiraterone) available to those in the ADT arm upon progression.

Table 22. Distribution of subsequent treatments for those making the transition to first, second, and third line post-progression treatment (Source, Company model).

	Darolutamide + ADT arm			**ADT arm**		
Treatment	**First-line**	**Second-line**	**Third-line**	**First-line**	**Second-line**	**Third-line**

No treatment/BSC	17.5%	35.0%	80.0%	3.5%	15.0%	50.0%
ADT	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Abiraterone	2.5%	5.0%	2.5%	42.5%	5.0%	2.5%
Enzalutamide	0.0%	0.0%	0.0%	42.5%	5.0%	2.5%
Docetaxel	60.0%	15.0%	0.0%	10.0%	50.0%	5.0%
Radium-223	20.0%	20.0%	7.50%	1.5%	20.0%	20.0%
Cabazitaxel	0.0%	25.0%	10.0%	0.0%	5.0%	20.0%
Bicalutamide	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Sum	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Rather than explicitly modelling progression through a series of mCRPC sub-states, the company calculated the expected costs of all subsequent lines of therapy in each arm and applied this as a one-off cost to the proportion leaving the nmCRPC state in each cycle of the model. The proportion of patients expected to transition to each subsequent line of therapy was approximated as the proportion of patients alive at the expected time of exit from the nmCRPC state and from subsequent lines of therapy. The mean time of exit from the nmCRPC state was informed by the selected MFS curves in each arm, and the expected durations for subsequent treatments were informed by external estimates of median times to treatment discontinuation. Thus, expected proportions of patients making transitions to subsequent lines of therapy accounted for expected differences in MFS and differences in the distribution of subsequent treatments and their median durations. The proportions receiving subsequent lines of therapy in the company base case are summarized in Table 23. The inferred times spent in subsequent lines of therapy were summarized in Table 21 above.

Table 23. Proportion of patients assumed to transition to first, second and third lines of subsequent therapy in the company's base case (Source: Company's economic model)

	Darolutamide + ADT arm	**ADT arm**
Proportion of patients that have first progression	0.727	0.872
Proportion of patients that have second progression	0.693	0.735
Proportion of patients that have third progression	0.640	0.666

Whilst the ERG believes the company's approach provides a reasonable approximation of subsequent treatment costs within the confines of the part-SA model structure, the approach is associated with some uncertainty:

- The proportion of the cohort alive at the mean time of exit from nmCRPC state only approximates the proportion of patients that transition to mCPRC. However, depending upon the relationship between progression status, time and mortality, it may in offer a conservative estimate.
- Assuming that time on subsequent therapies equates with the time to the next subsequent therapy ignores that the fact that progression can occur sometime after treatment discontinuation.
- Use of median times on treatment to model the proportion of patients reaching second and third line therapies may overestimate the rate of progression to these subsequent lines.
- There is no explicit link in the model between the assumed rate of progression through mCRPC treatment lines for costing purposes, and the expected rate of progression through mCRPC sub-states underpinning the mCRPC utility weight.
- Given the Part-SA approach, there is no modelled link between the use of different subsequent treatments and mCRPC life years as a whole – which leads to a somewhat counterintuitive finding that post-progression survival is greater in the darolutamide arm, despite less effective treatments being available to progressed patients in this arm of the model.
- Proportionally, more darolutamide patients receive inexpensive BSC within mCRPC 1-3 as well as a prolonged period of time in a 4th line (BSC) state (Table 21). The length of the 4th line state is longer due to time in the PPS state being dependent on the selected MFS and OS curves, rather than the expected efficacy of subsequent treatments.
- The increased mCRPC life years in the darolutamide arm, which are achieved at lower cost compared to those in the ADT arm, lack face validity. This has a downward impact on the ICER. The greater the difference between the selected MFS and OS curves, the greater the length of time in the inexpensive BSC (fourth-line) sub-state of mCRPC, and the total time in the mCRPC state overall.

The last point was discussed in more detail in section 4.2.6 above and will be explored further in scenario analyses through adjustments to the chosen OS and MFS curves for darolutamide plus ADT and ADT alone.

The unit costs applied for the acquisition of subsequent treatments are detailed in Table 45 of the company submission. They included a PAS available for radium-223, but did not incorporate PAS prices available for abiraterone, enzalutamide and cabazitaxel. Therefore, the ERG will produce a confidential appendix inclusive of the appropriate PAS prices.

Monitoring costs of the nmCRPC and mCRPC states

The company assumes equal health care resource use across treatment arms in both the nmCRPC and mCRPC health states, which is consistent with TA580 and the assumption of equal monitoring frequency for mCRPC by treatment arm in TA377. The ERGs clinical expert broadly supported this assumption.

Monitoring costs were informed by a retrospective cohort study led by IQVIA and funded by Bayer (Company submission, document B, page 140). The primary outcome of the study is the per cycle frequency of different monitoring events (see Table 38 of the company submission, document B).

The per cycle probability of events was determined using just 44 patients diagnosed with nmCRPC between January, 1st 2011 and January, 1st 2019. It can be noted that the sample was small and was recruited over a wide time interval which may have seen substantial changes in clinical practice. Therefore, the ERG has some concerns that the study may not provide robust estimates of health care resource use for the current patient population. The frequencies of certain monitoring tests such as CT scans seemed particularly low. In addition, the ERG's clinical expert advised that patients with nmCRPC and mCRPC would tend to have an outpatient appointment every 6 weeks, and alternate between consultant led and nurse led appointments.

[redacted] Thus, based on its clinical experts' opinion, the ERG

tends to prefer resource use frequencies applied in TA580, which were also broadly consistent with assumptions applied in TA377 for mCRPC patients. See appendix 1 for the comparison of the CS monitoring frequencies against those of TA580.

With respect to the unit costs applied to resource use elements, the ERG finds the majority to be reasonable. The use of the general PSSRU 2019 outpatient appointment cost for consultant oncologist outpatient visits, rather than the HRG cost, was queried in the clarification letter; the company presented a scenario where a value of £194.17 was used from the HRG (CL Non-Admitted Face-to-Face Attendance, Follow-up code 370). This resulted in a small increase of the ICER (see Table 20 of the company response to the clarification letter).

End of life care costs

End-of-life care costs are applied as a one-off cost of £7,761 upon entry to the death state to represent the terminal care costs over the last 3 months of life. This is comprised of: district nurse visits, nursing and residential care, hospital care and Marie Curie nursing service. This total is taken from a report by Georghiou and Bardsley 2014.[38] As discussed in the report, we should expect cancer patients to use more hospital resources and less nursing and residential care in comparison to the general population. Therefore, the report produced separate costs for the cancer population and for the general population. Furthermore, the cost used in the company base case does not include the cost of GP contact which is a constituent of the terminal care costs estimated by Georghiou and Bardsley. The full terminal care cost for cancer patients from the report, after adjusting for inflation, is £8,804. The impact of this on the company's base case ICER is minimal as it is only the timing of the cost that varies by treatment arm.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

At the time of the original submission, the company presented a base case ICER for darolutamide plus ADT versus ADT alone of £11,445 per QALY gained. This was based on expected incremental cost of £21,374 per patient for an expected QALY gain of 1.87 (see Table 49 of the CS, document B). In response to the clarification letter, the company submitted a revised base case incorporating the following changes:

1. Revised OS curves for darmolutamide plus ADT and ADT alone, and a revised ToT curve for darolutamide based on the more recent (November 2019) data cut from ARAMIS.
2. Correction of two formula inconsistencies in the "Subseq_TrT" (cells E92-E93) and "Parameter" (D182-D183 and D202-D203) worksheets of their model.
3. Treatment arm specific mCRPC utility values, to account for expected between arm differences in the subsequent treatment distribution.
4. A revised approach to discounting the costs of subsequent treatments in the mCRPC state.
5. A revised approach to discounting treatment costs, to account for the dispensing of medication at the start of each model cycle.
6. Revisions to account for the ongoing background use of ADT throughout the entire model time horizon.

In their response to the clarification letter, the company provided analyses that showed the impact of each change applied to their original base case and the combined impact of all changes in their revised base case. They also showed the impact of individual changes 2 to 5 (above) after updating the OS and ToT curves based on the Nov 2019 data cut. Table 24 below summarises the impact of these changes on the company's original ICER. For transparency, the impact of changing the OS curves and the ToT curve (combined in single change by the company) are shown separately in Table 24. It can be noted that updating of the darolutamide ToT

curve had the largest individual impact on the ICER. As mentioned above, the ERG has concerns that this curve was updated without also updating the MFS curves to the same data cut.

The full revised deterministic company base case results are provided in Table 25 below. Note, the probabilistic ICER was very close to the deterministic ICER (Company submission, Appendix N, Table 9).

It should be noted all that these results incorporate PAS discounts for darolutamide and radium-223, but not the PAS discounts available for enzalutamide, abiraterone and cabazitaxel. For this reason, the ERG will provide a confidential PAS (cPAS) appendix that incorporates all relevant PAS discounts.

Table 24. Company's original base case and revisions incorporated in their new base case

Scenario		**ICER (£/QALY): darolutamide +ADT versus ADT**	**Percentage change to ICER**
Submitted company model base case		£11,445	
i.	Revised OS curves based on Nov 2019 data cut	£11,865	3.66%
ii.	Revised ToT curve based on Nov 2019 data cut	£7,384	-35.48%
iii.	Combined revisions to OS and ToT curves based on Nov 2019 data	£6,296	-44.99%
iv.	Corrections to formulae	£10,159	-11.23%
v.	Revised treatment arm specific mCRPC utility values	£12,059	5.58%
vi.	Revised approach to discounting the costs of subsequent treatments	£11,549	0.91%
vii.	Revised approach to discounting treatment costs	£11,475	0.26%

Scenario	ICER (£/QALY): darolutamide +ADT versus ADT	Percentage change to ICER
viii. Amendments for costing ongoing background use of ADT	£11,835	3.41%
Revised company base case incorporating all changes	£4,919	-57.02%

Table 25. Company's revised base case results darolutamide (with PAS) + ADT versus ADT - updated company model in line with ERG clarification questions and utilising unadjusted OS and ToT data from the Nov 2019 final data-cut (Source: Table 8, Appendix N of the CS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Total MFS LYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental MFS LYs	ICER (£/QALY)	Cost per MFS month gained
ADT	[redacted]	[redacted]	[redacted]	[redacted]						
Darolutamide + ADT	[redacted]	[redacted]	[redacted]	[redacted]	£6,165	1.65	1.25	1.81	£4,919	£284

Key: ADT, androgen deprivation therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; MFS, metastasis-free survival; PAS, patient access scheme; QALYs, quality-adjusted life years.

5.2 Company's sensitivity analyses

The company provided one-way sensitivity analysis and a range of scenario analyses as part of their submission, and these were subsequently updated relative to the company's revised base case (see, appendix N, company submission, Figure 25 and Table 10).

The one-way sensitivity analysis indicated that the ICER was quite sensitive to the proportion of patients progressing to a first subsequent treatment, and the subsequent treatment durations applied for enzalutamide and abiraterone. It should be borne in mind that subsequent treatments did not have appropriate PAS discounts applied in these analyses. Nevertheless, post progression treatment costs in relation to post-progression benefits are likely to be quite important drivers in the model.

The scenario analyses support the importance of subsequent treatment costs, with scenarios assuming subsequent therapies in line with observed data from ARAMIS generating the highest ICERs. However, the subsequent treatment distributions in ARAMIS are not generalisable to the NHS, and a more pertinent uncertainty relates to whether the OS extrapolations of ARAMIS can be generalised to the NHS setting. The company did address this uncertainty to an extent by running a scenario in their original submission which equalised the hazard of mortality in the ADT arm to the hazard of mortality in the darolutamide arm from 8.7 years, forcing the OS curves to start converging from this time point. Upon request at the clarification stage, the company provided further scenarios which equalised the hazard mortality from 5 and 7 years, to the extrapolated hazard of mortality in the ADT arm and the darolutamide arm (results provided in section 6.2 below). The ERG prefers the scenarios that equalise mortality in the darolutamide arm to the mortality in the ADT arm. This is because the ERGs clinical expert believed the OS extrapolation for darolutamide to be overoptimistic and was more confident in the validity of the ADT OS extrapolation.

5.3 Model validation and face validity check

Section B.3.10 of Document B (page 183) summarises the validation checks of the model carried out by the company. This includes:

- Comparison of the model outputs to clinical trial data from ARAMIS and other published trials of antiandrogens for nmCRPC (SPARTAN and PROSPER).[33, 39]

- Quality control checks of the cost-effectiveness model.
- External clinical validation of the economic model by a panel of ten UK practicing clinicians on February 4th, 2020.

Comparison of model outputs to trial data

Document B, Appendix J, page 97 of the CS summarises the model predictions for Median MFS, OS and PPS life years for both arms of the model against clinical trial data from ARAMIS, SPARTAN (apalutamide) and PROSPER (enzalutamide). The company note that at the time of submission, median OS had not been reached in any trials of antiandrogens in the nmCRPC population: ARAMIS, PROSPER or SPARTAN trial. The median MFS predicted by the model is broadly in line with the observed data from ARAMIS, in which median MFS was slightly higher in both the daroluatmide and placebo arms compared with the active treatment and placebo arms of PROSPER and SPARTAN.

Black-box verification checks

The company note that quality control of the model involved a review for coding errors, inconsistencies and plausibility of inputs. Prior to the submission of the clarification letter to the company, the ERG also conducted quality checks upon the model for coding errors and plausibility of inputs. In addition, the ERG conducted black box checks of the model as suggested by Tappenden and Chilcott (2014).[40] The results of this are reported in Table 26 for the updated model submitted at the clarification stage by the company.

Clinical advisory board

The company hosted an Advisory Board of ten clinical experts to help validate several of the inputs and assumptions in their economic model, including aspects of structure, analysis methods, curve selections, utility values and subsequent treatments. The input of the board into most of these issues has been acknowledged/discussed in the relevant preceding sections. Below the ERG note some outstanding issues related to analysis methods for MFS, not discussed above, and curve selections that may benefit from further discussion and scrutiny.

Analysis for patients found to have metastasis at baseline

The company note that that clinical advisors reached consensus that censoring participants found to have metastasis at baseline (BMC) offered the most conservative analysis approach

for MFS but their clinical advisers also noted that some patients with metastases would be missed in practice, suggesting some support for BME analysis. The ERG does agree with the company's use of BMC analysis to limit the impact of misdiagnosed patients on the outcome of interest, and further notes that the event of misdiagnosing some metastatic patients as non-metastatic may become less likely over time with the use of PET scans in routine care.

Clinical advisory board: Extrapolation of survival curves

The selected survival curves were validated by the company using a clinical advisory board. However, the advisory board report does note that the advisors "[redacted]" and that their selections were partly based on alignment of extrapolations "[redacted]". The ERG believe that uncertainty remains around the validity of the long-term extrapolations of OS, and the company note that their advisors suggested exploration [redacted]. The ERG clinical expert is of the opinion that the Weibull curve may be too optimistic with respect to long-term OS for a CRPC population, and would not expect any patients to still be alive by 20 years (discussed in section 4.2.6 above)**.** Further potential validity issues that have not been scrutinised by clinical experts relate to: 1) the updating of OS and ToT curves using a November 2019 data cut, whilst retaining the original MFS curves from the September 2018 data cut; 2) the plausibility of the model projections of expected life years accruing in the mCRPC state once patients progress. The uncertainties relating to these issues were discussed in section 4.2.6.

Table 26. Results of the black box verification checks carried out by the ERG

Model component	Model test	Unequivocal criterion for verification	Issues identified in company model
Clinical trajectory	Set relative treatment effect (odds ratios, relative risks or hazard ratios) parameter(s) to 1.0 (including adverse events)	All treatments produce equal estimates of total LYGs and total QALYs	None
	Sum expected health state populations at any model timepoint (state transition models)	Total probability equals 1.0	None
QALY estimation	Set all health utility for living states parameters to 1.0	QALY gains equal LYGs	None
	Set QALY discount rate to 0	Discounted QALYs = undiscounted QALYs for all treatments	Not tested as model only reports one QALY output with the discount rate applied.
	Set QALY discount rate equal to very large number	QALY gain after time 0 tend towards zero	None
Cost estimation	Set intervention costs to 0	ICER is reduced*	None
	Increase intervention cost	ICER is increased*	None
	Set cost discount rate to 0	Discounted costs = undiscounted costs for all treatments	None
	Set cost discount rate equal to very large number	Costs after time 0 tend towards zero	None

Model component	Model test	Unequivocal criterion for verification	Issues identified in company model
Input parameters	Produce n samples of model parameter m	Range of sampled parameter values does not violate characteristics of statistical distribution used to describe parameter.	Sample tested. No issues found.
General	Set all treatment-specific parameters equal for all treatment groups	Costs and QALYs equal for all treatments	None. For the model structure to allow this the drug cost of Darolutamide must be set to £0.
	Amend value of each individual model parameter*	ICER is changed	None. Parameters behave as expected under the model structure.
	Switch all treatment-specific parameter values*	QALYs and costs for each option should be switched	No issues found in terms of QALY outcomes. The model structure does not allow this with regard to costs. This is of no concern as the ADT-only arm does not have a ToT curve since patients receive ADT for the entire model time horizon.

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

In addition to the scenario analyses conducted by the company, the ERG conducted some further scenario analyses to explore identified uncertainties in the modelling assumptions. Table 27 summarises the scenarios and Table 28, in Section 6.2, provides results from deterministic analysis of the scenarios.

Table 27. Scenarios include in the ERG's cost effectiveness analysis

No	Scenario analysis	Scenario description	Justification
	Reference scenario: Company revised base case	Company base case incorporating the revisions listed in the company response to the clarification letter, including Nov 2019 data cut for OS and ToT.	The company's revised updated case represents the company's preferred analysis
Darolutamide ToT curve			
1	Weibull extrapolation of Nov 2019 darolutamide ToT	Apply the fitted Weibull curve from the Nov 2019 darolutamide ToT data.	The Weibull curve was originally suggested as a plausible extrapolation of the Oct 2018 ToT data, and it remains a good statistical fit to the Nov 2019 ToT data.
2	Weibull extrapolation of Oct 2018 darolutamide ToT	Apply fitted Weibull curve for the Oct 2018 darolutamide ToT data	Assessed for consistency with the MFS data used in the model, and because some clinical experts suggested the Weibull offered a plausible extrapolation of the Oct 2018 ToT data.
MFS curves			
3	Gompertz curves for MFS	Apply fitted Gompertz curves for MFS in both treatment arms	Updating the ToT curve for darolutamide using Nov 2019 data shifted it downward, which might reflect higher rates of progression in the latter data cut. However, the revised model retained the MFS curves

No	Scenario analysis	Scenario description	Justification
			from the earlier October 2018 data cut, potentially introducing bias. Therefore, the ERG believes a scenario testing the most pessimistic MFS curves from the Oct 2018 data cut, in combination with the revised ToT curve from Nov 2019, is justified.
4	Downward adjustment of MFS curves (based on ToT Gompertz)	Applies a proportional adjustment to the company's preferred MFS curves, using cycle specific hazard ratios between the preferred Gompertz extrapolations of the Nov 2019 and Oct 2018 darolutamide ToT data.	Updating the ToT curve for darolutamide, using Nov 2019 data, shifted it downward – possibly reflecting higher rates of progression in the latter data cut. However, the revised model retained the MFS curves from the earlier October 2018 data cut, potentially introducing bias. Therefore, the ERG believes the impact of a similar downward adjustment to the MFS curves should be explored.
5	Downward adjustment of MFS curves (based on ToT Weibull)	Applies a proportional adjustment to the company's preferred MFS curves, using cycle specific hazard ratios between the Weibull extrapolations of the Nov 2019 and Oct 2018 darolutamide ToT data.	As above. And adjustment of MFS using the difference between the Weibull extrapolations of ToT (Nov 2019 versus Oct 2018) is justified since the Weibull curve was originally suggested as a plausible extrapolation of the Oct 2018 ToT data.
OS curves			
6	Equalise mortality risk in the darolutamide arm to the mortality risk in the ADT ARM from 5 years	Sets the mortality hazard in the darolutamide arm equal to that in the ADT arm from 5 years onwards	There is uncertainty around assumed long-term proportional reduction in the hazard of mortality with darolutamide versus ADT, since patients in the darolutamide arm have access to more

No	Scenario analysis	Scenario description	Justification
			effective treatments once they progress. Five years marks the limit of observed survival data in ARAMIS.
7	Equalise mortality risk in the darolutamide arm to the mortality risk in the ADT ARM from 7 years	Sets the mortality hazard in the darolutamide arm equal to that in the ADT arm from 7 years onwards	There is uncertainty around assumed long-term proportional reduction in the hazard of mortality with darolutamide versus ADT, since patients in the darolutamide arm have access to more effective treatments once they progress.
8	Equalise mortality risk in the ADT arm to the mortality risk in the darolutamide arm from 5 years	Sets the mortality hazard in the ADT arm equal to that in the darolutamide arm from 5 years onwards	As for 6 and 7 above.
9	Equalise mortality risk in the ADT arm to the mortality risk in the darolutamide ARM from 7 years	Sets the mortality hazard in the ADT arm equal to that in the darolutamide arm from 7 years onwards	As for 6 and 7 above.
10	Generalised gamma for OS in the darolutamide arm	Applies the generalised gamma extrapolation of darolutamide OS (Nov 2019 data). Retains the Weibull extrapolation for ADT alone.	The ERGs clinical expert believed the Weibull extrapolation was reasonable for ADT alone, but optimistic for darolutamide plus ADT. This scenario therefore assesses the next more pessimistic extrapolation of darolutamide OS.
11	Average of generalised gamma and Weibull for OS in the darolutamide arm	Takes the average cycle specific hazard of mortality from the generalised gamma and Weibull extrapolations of darolutamide OS (Nov 2019 data). Retains the	The ERGs clinical expert believed the Weibull extrapolation was reasonable for ADT alone, but optimistic for darolutamide plus ADT. He further noted that a curve lying between the Weibull and the more pessimistic generalised gamma would offer a more

No	Scenario analysis	Scenario description	Justification
		Weibull extrapolations for ADT alone.	reasonable extrapolation for this population.
Costs			
12	Alternative monitoring costs (TA580)	Application of health state resource use frequencies from TA580 (appendix 1), with community nurse visits removed to avoid double counting ADT admin costs	ERG clinical expert advised that these frequencies appeared more in keeping with current NHS practice.
13	Alternative monitoring costs (TA580) with revised unit costs for consultant oncology visits and ADT administration	Applies changes in scenario 12 with alternative unit costs for administration of ADT from TA404 and oncology specific outpatient visits	The ERG believe these unit costs are more appropriate than the generic costs per hour applied in the company base case.
14	Inclusion of cardiac disorders adverse event cost and utility impact	Applies the percentage of patients experiencing any cardiac event, and the cost and utility impact of MACE events taken from TA580.	Cardiac disorders are an adverse event category of special interest with ADT or novel antiandrogens. Although the company note that darolutamide was not found to increase the risk, the percentage experiencing a cardiac event of some sort was above 5% in both arms and directionally higher in the darolutamide arm (11.8% versus 7.4%). The ERG therefore believe that the impact of their inclusions warrants exploration.
15	Increased end of life care costs	Increases the terminal care costs from £7,761 to £8,804.	From the reference provided by the company, the full terminal care cost for cancer patients, after adjusting for inflation, is £8,804
Combinations			
16	1,3, and 6		
17	1,3, and 7		

No	Scenario analysis	Scenario description	Justification
18	1,3, and 11		
19	12, 13, and 15		

Note: Scenarios 6, 7, 8 and 9 were provided by the company at the clarification stage

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

It can be noted from the additional scenarios assessed by the ERG, that the ICER increases with curve selections which push the MFS and ToT curves for darolutamide closer together (Table 28, scenarios 1-5). The scenarios that adjust down the OS survival gain for darolutamide plus ADT versus ADT alone have a somewhat counterintuitive impact of reducing the ICER, which is driven by a greater reduction in the incremental costs in relation to the reduction in the incremental QALY (Table 28, scenarios 6-11). Changes to the monitoring frequencies has a modest downward impact on the ICER (scenario 12), though changing the follow-up OP unit costs and ADT admin costs partly reverses this (scenario 13).

Table 28. ERG scenario analysis results

No.	Description	Darolutamide + ADT			ADT alone			
		Costs	QALY	LYG	Costs	QALY	LYG	ICER vs ADT
	Reference scenario: Company revised base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,919
1	Weibull extrapolation of Nov 2019 darolutamide ToT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,102
2	Weibull extrapolation of Oct 2018 darolutamide ToT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,512
3	Gompertz curves for MFS (both)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,153
4	Downward adjustment of MFS curves (based on ToT Gompertz)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,254
5	Downward adjustment of MFS curves (based on ToT Weibull)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,555
6	Equalise mortality risk in the darolutamide arm to the mortality risk in the ADT ARM from 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Darolutamide dominant
7	Equalise mortality risk in the darolutamide arm to the mortality risk in the ADT ARM from 7 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,554
8	Equalise mortality risk in the ADT arm to the mortality risk in the Darolutamide arm from 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£983
9	Equalise mortality risk in the ADT arm to the mortality risk in the Darolutamide ARM from 7 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,486
10	Generalised gamma for OS in the darolutamide arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Darolutamide dominant
11	Average of generalised gamma and Weibull for OS in the darolutamide arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,398
12	Alternative monitoring costs (TA580 with community nurse visits removed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,441

No.	Description	Darolutamide + ADT			ADT alone			
		Costs	QALY	LYG	Costs	QALY	LYG	ICER vs ADT
13	Alternative monitoring costs with HRG consultant costs and alternate ADT admin cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,706
14	Inclusion of cardiac disorders adverse event cost and utility impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,088
15	Increased end of life care costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,872
16	1,3, and 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,725
17	1,3, and 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,446
18	1,3, and 11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,306
19	12, 13, and 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,658

6.3 ERG's preferred assumptions

The ERG's preferred assumptions are as follows:

i. Given the relative immaturity of the OS data from the ARAMIS trial (median OS not reached), and uncertainty regarding the generalisability of the OS benefit and the long-term extrapolations, the ERG prefers scenarios that equalise the hazards of mortality from a future timepoint beyond the trial follow-up period. The ERG acknowledges that selection of a cut-off for the relative mortality benefit is somewhat arbitrary, but are guided by their clinical expert's expectation that OS would be zero by 20 years in both arms. Further, the ERG believes the selection should result in undiscounted mCRPC life years being greater in the ADT arm of the model. Five years is applied in the ERG base case, and seven years is also explored.

ii. Since updating of darolutamide ToT analysis resulted in a downward shift in the curve (due to more censoring events being replaced with discontinuation events), and MFS was not updated to the corresponding data cut, the ERG prefers to adopt a more pessimistic extrapolation of MFS. This assumes a similar downward shift in the MFS curve might have been observed had it also been updated to the same data cut. To account for this, the Gompertz curve is selected for both treatment arms. The ERG acknowledges the uncertainty in this revision, and suggest that this uncertainty would be better addressed by updating MFS to the same data cut as ToT and OS.

iii. Application of the health care resource use estimates from TA580.

iv. Application of alternative ADT administration costs (inflated from TA404), and oncology outpatient visit costs (NHS reference costs for oncology specialty, rather than the PSSRU average outpatient unit cost) (section 4.2.8, p55, p59)

v. Application of alternative cancer specific end of life costs, ADT administration costs, and oncology outpatient visit costs (section 4.2.8, page 59).

The cumulative impact of these combined changes is shown in Table 29. The deterministic ICER for darolutamide plus ADT versus ADT alone comes to £8,429 per QALY gained (Table 2). These results include the PAS discount for darolutamide and Radium-223, but do not include available discounts for other subsequent therapies. Further scenarios referencing the ERG base case illustrate the impact of further uncertainty around the OS and ToT extrapolations. Modelled MFS, OS and ToT curves for the ERG base case are shown in Figure 6.

Table 29. ERG's preferred model assumptions

No.	Description	Darolutamide + ADT			ADT alone			
		Costs	QALY	LYG	Costs	QALY	LYG	ICER vs ADT
i.	Gompertz for September 2018 MFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,153
ii.	Equalise mortality to ADT arm from 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,406
iii.	Revised monitoring costs from TA580	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,210
iv	Oncology specific OP visit unit cost and revised ADT admin unit cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,477
v.	Revised terminal care costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,429
Further scenarios on ERG base								
	ERG base	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,429
1	Equalise mortality to ADT arm from 7 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,819
2	Average of Nov 2019 generalised gamma and Weibull for darolutamide OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,318
3	Weibull extrapolation of Nov 2019 darolutamide ToT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,748

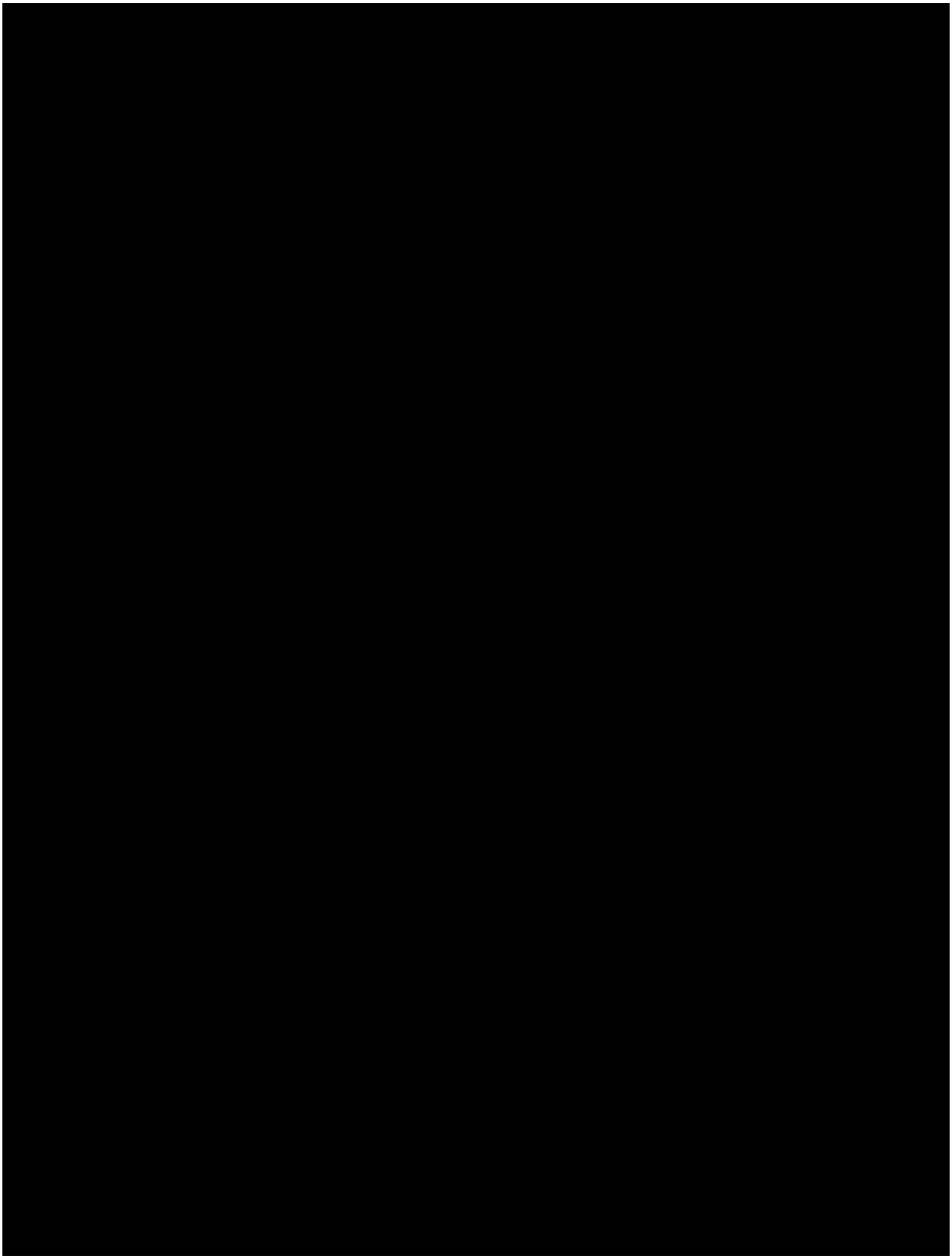

Figure 6. ERG base case extrapolations of OS, MFS and ToT for the a) darolutamide plus ADT and b) ADT arms

6.4 Conclusions of the cost effectiveness section

The ERG believes the following to the be the key issues and uncertainties in the cost-effectiveness evidence:

1. The model structure, which collapses up to three lines of subsequent active therapy into a single mCRPC health state, leads to some uncertainty around progressed health state utility and subsequent treatments costs. However, the ERG believes the company has provided a reasonable approximation in the context of the Part-SA model.
2. The company updated their OS and ToT curves to a latter November 2019 data cut at the clarification stage, but retained the MFS curves from the earlier September 2018 data cut in their revised base case. The ERG is concerned that combining curves from different data cuts generates additional uncertainty, particularly with respect MFS and ToT, where the update has resulted in greater divergence between these curves, greatly reducing the darolutamide treatment costs in the nmCRPC health state.
3. The generalisability of the ARAMIS trial OS benefit for darolutamide plus ADT versus ADT alone, to the modelled NHS treatment pathway. This is because subsequent treatments in the ARAMIS differed from the suggested subsequent treatment distribution in NHS routine clinical practice.
4. Related to the point 3, The ERG believes the OS extrapolation for darolutamide plus ADT may be overoptimistic, leading to a life-year (LY) and quality-adjusted life-year (QALY) gain that lacks face validity. In particular, the ERG questions the face validity of patients in the darolutmide arm accruing more undiscounted life years in the mCRPC health state compared to patients in the ADT arm, when patients in the ADT arm have greater access to subsequent treatments that have been shown in previous trials and appraisals to increase OS in the mCRPC health state. The mechanism driving this, is an increasing proportional reduction in the hazard of mortality favouring darolutamide across the entire time horizon of the model.
5. The monitoring costs applied to the nmCRPC and mCRPC health states are based on a small sample of NHS patients recruited over a relatively wide time interval (2011 – 2019), and some elements of resource use frequency appear low compared to estimates previously accepted in relevant submissions (e.g. TA580 and TA377).

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Appendix 1 Frequency of monitoring events per 28-day cycle for both treatment arms used in company base case (IQVIA study) and ERG preferred base case (TA580).

Resource	Frequency/rate per 28 days			
	nmCRPC		mCRPC	
	Company base case (IQVIA study)	TA580	Company base case (IQVIA study)	TA580
Outpatient visit - Consultant	[redacted]	0.33	[redacted]	0.33
Outpatient visit - nurse	[redacted]	0.33	[redacted]	0.33
Community nurse visit	[redacted]	0.67	[redacted]	0.67
A&E visit	[redacted]	0.00	[redacted]	0.00
CT scan	[redacted]	0.33	[redacted]	0.33
Bone scan	[redacted]	0.04	[redacted]	0.04
Full blood count	[redacted]	0.50	[redacted]	0.50
Liver function test	[redacted]	0.50	[redacted]	0.50
Kidney function test	[redacted]	0.50	[redacted]	0.50
PSA count	[redacted]	0.50	[redacted]	0.50
Testosterone test	[redacted]	0.00	[redacted]	0.00
Metabolic panel/ biochemistry	[redacted]	0.00	[redacted]	0.00
Blood and electrolytes	[redacted]	0.00	[redacted]	0.00
Bone profile	[redacted]	0.00	[redacted]	0.00
X-ray	[redacted]	0.00	[redacted]	0.00
Inpatient hospitalizations-overnight admission	[redacted]	0.00	[redacted]	0.00
Inpatient hospitalizations-day case	[redacted]	0.00	[redacted]	0.00