NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:
The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from **Bayer**

2. **Company response to NICE's request for clarification**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Prostate Cancer UK
   b. Tackle Prostate Cancer

4. **Expert personal perspectives** from:
   Stephen Allen, Tackle Patient Representative – patient expert, nominated by Tackle Prostate Cancer
   Stephen Allen supports the statement from Tackle Prostate Cancer and will not be submitting an individual statement

5. **Evidence Review Group report** prepared by **Aberdeen HTA Group**

6. **Evidence Review Group – factual accuracy check**

7. **Technical engagement response** from **Bayer**
   a. Technical engagement response from company
   b. Technical engagement response appendix

8. **Technical engagement responses from experts:**
   a. Professor Amit Bahl, Bristol Haematology and Oncology Centre, University Hospitals Bristol and Weston NHS Trust – clinical expert, nominated by Bayer

9. **Technical engagement response from consultees and commentators:**
   a. Prostate Cancer UK
   b. Tackle Prostate Cancer

10. **Evidence Review Group critique of company response to technical engagement** prepared by **Aberdeen HTA Group**

11. **Final Technical Report**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Document B

Company evidence submission

13 March 2020

File name	Version	Contains confidential information	Date
ID1443_Darolutamide + ADT in nmCRPC NICE STA Document B_redacted v1.1	Version 1.1	No	03.07.2020

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Tables and figures

B.1. Decision problem, description of the technology and clinical care pathway

B.1.1. Decision problem

This submission covers darolutamide's (NUBEQA®) full anticipated marketing authorization: adult men with non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease. In this submission 'high risk' is defined as an absolute prostate specific antigen (PSA) level ≥2 ng/mL and a prostate specific antigen doubling time (PSADT) of ≤10 months. This definition aligns with the key clinical trial informing efficacy for darolutamide, previous appraisal in this indication (1, 2) and clinical experts' opinion from an advisory board held by Bayer (3).

Although the final scope issued by the National Institute for Health and Care Excellence (NICE) describes the population as adults with non-metastatic hormone-relapsed prostate cancer (nmHRPC), in this submission, we consider HRPC and castration-resistant prostate cancer (CRPC) as synonymous. However, to align with the exact wording in the anticipated European summary of product characteristics (SmPC), we refer to the indication as adult men with nmCRPC.

Table 1: The decision problem

	Final scope issued by NICE	**Decision problem addressed in the company submission**	**Rationale if different from the final NICE scope**
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
Intervention	Darolutamide + ADT	Darolutamide + ADT	Not applicable
Comparator(s)	Androgen deprivation therapy	Androgen deprivation therapy	Not applicable
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
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

B.1.2. Description of the technology being appraised

A summary description of darolutamide is provided in Table 2. The draft SmPC is provided in Appendix C. The European public assessment report will be shared as soon as it becomes available.

Please note – the summary of product characteristics is draft, pending finalisation of the marketing authorisation application process.

Table 2: Technology being appraised

UK approved name and brand name	Darolutamide (Nubeqa®)
Mechanism of action	Darolutamide is an androgen receptor (AR) inhibitor with a flexible polar-substituted pyrazole structure that binds with high affinity directly to the receptor ligand binding domain. Darolutamide competitively inhibits androgen binding, AR nuclear translocation, and AR-mediated transcription (4, 5) – components of the AR signalling pathway, which is the main driver of castration resistant prostate cancer (CRPC) (6, 7). Treatment with darolutamide decreases prostate tumour cell survival and proliferation leading to potent antitumour activity. Keto-darolutamide, a major metabolite of darolutamide, also exhibits similar in vitro activity to darolutamide.
Marketing authorisation/CE mark status	Positive CHMP opinion was adopted on 30/01/2020 and EC decision is expected at the end of March 2020.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Treatment of adult men with non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease. See Appendix C for draft SmPC.
Method of administration and dosage	The recommended dose of darolutamide is 600 mg (two 300 mg film-coated tablets) taken orally, twice daily, equivalent to a total daily dose of 1200 mg. Tablets should be swallowed whole and taken with food. In patients with 1) severe renal impairment (eGFR 15–29 mL/min/1.73 m^2) not receiving haemodialysis, or 2) moderate hepatic impairment (Child-Pugh Class B) the recommended dose of darolutamide is 300 mg twice daily (equivalent to a total daily dose of 600 mg).

	Patients receiving darolutamide should also receive a gonadotropin-releasing hormone (GnRH) analogue concurrently or should have had a bilateral orchidectomy.
Additional tests or investigations	None. Identification of patients with non-metastatic CRPC would occur as part of the PSA monitoring within current clinical practice. This would include any necessary scans prompted by PSA monitoring.
List price and average cost of a course of treatment	The indicative list price is £4,040 (per 112 x 300 mg tablets) for a 28-day supply. Average cost of a course of treatment: [redacted]
Patient access scheme (if applicable)	There is a confidential discount of [redacted] applied to the list price currently under consideration with the PASLU.
CHMP=Committee for Medicinal Products for Human Use; EC=European Commission;	

B.1.3. Health condition and position of the technology in the treatment pathway

Darolutamide is indicated for the treatment of adult men with non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease.

Prostate cancer

According to the latest provisional release of cancer registration statistics by Public Health England, in 2018, prostate cancer became the most common cancer in England, and the most common form of cancer affecting men, with around 49,000 new prostate cancer cases diagnosed (8). In 2017, there were 10,146 prostate cancer-related deaths in England (9); approximately 7% of all cancer deaths. An ageing population combined with increasing public awareness means more men are being diagnosed with the disease.

Prostate cancer survival has markedly improved over the last 40 years in the UK, likely due to the availability of prostate-specific antigen (PSA) testing. In the earliest stages of prostate cancer, patients are typically asymptomatic at diagnosis. When diagnosed at its earliest stage, men with prostate cancer have a 5-year survival rate

of 100%, compared with a 5-year survival rate of 49% when the disease is diagnosed at advanced stages (10). Presentation with advanced disease may include symptoms such as urinary outflow obstruction, urinary urgency or frequency, haematuria, pelvic or back pain due to bone metastases (11). Metastases are a major cause of complications and death among men with prostate cancer and most develop metastases to lymph nodes, bone or visceral sites, such as the lung and liver (12). Bone metastases are associated with multiple complications such as bone pain, pathologic fractures, and skeletal-related events (SREs) such as spinal cord compression (13).

The main risk factors for prostate cancer are age (>50 years; prostate cancer is most common in men aged 75-79 years), ethnicity (black African-Caribbean males) and a family history of prostate cancer (14).

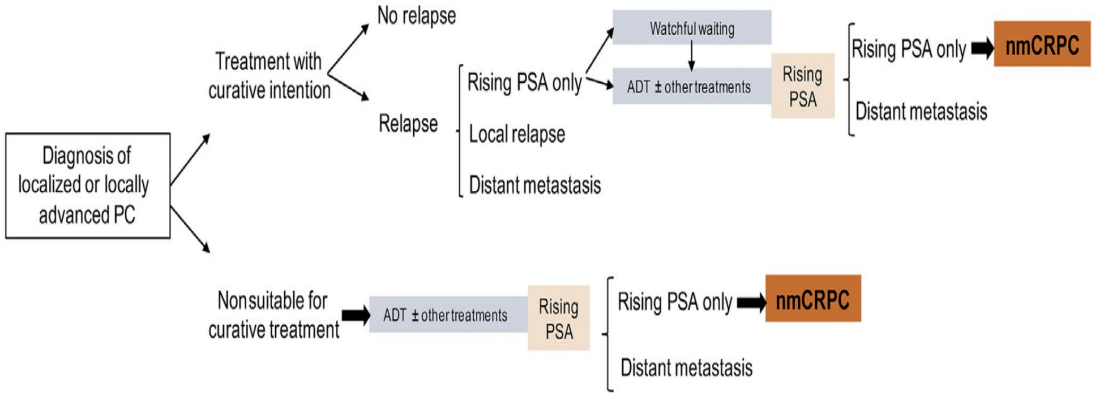
Treatment strategies are focused around eradicating the primary tumour, increasing progression-free survival, reducing mortality, and improving quality of life (15). Treatment decisions are guided by baseline prostate specific antigen (PSA) levels and kinetics (velocity / doubling time), tumour grade (Gleason score), stage and risk of progression. Other factors include patient preference, performance status, co-morbid conditions and life expectancy.

At the time of diagnosis in an early stage or non-metastatic setting, many prostate cancer patients receive localised treatment which may be curative (i.e. radical prostatectomy and / or radiotherapy), and / or androgen deprivation therapy (ADT). Prostate cancer cells usually need testosterone to grow, therefore ADT involves either 1) stopping the production of testosterone (via orchidectomy, luteinising hormone-releasing hormone [LHRH] agonists, or gonadotrophin releasing hormone [GnRH] antagonists) or 2) blocking the effect of testosterone on prostate cancer cells, by use of antiandrogen treatment. Prostate cancer that is responsive to ADT is often termed ‘hormone-sensitive’ prostate cancer. Patients who relapse (i.e. rising PSA) following surgery or radiotherapy are also treated with ADT (see Figure 1).

Non-metastatic castration resistant prostate cancer (nmCRPC)

Despite high initial response rates of 80-90%, nearly all patients develop progressive disease following ADT – a disease state commonly referred to as castration-resistant prostate cancer (CRPC) or hormone-relapsed prostate cancer (HRPC) (16). Usually, the earliest sign of resistance to ADT is a rising serum PSA level with an absence of metastases on conventional imaging (computed tomography [CT], magnetic resonance imaging [MRI], bone scan [BS]). This stage of disease is classified as nonmetastatic, castration-resistant prostate cancer (nmCRPC) (12). The Prostate Cancer Clinical Trials Working Group 3 (PCWG3) defines this PSA only failure as '*a rising PSA that is greater than 2ng/mL higher than the nadir; the rise has to be at least 25% over nadir, and the rise has to be confirmed by a second PSA at least three weeks later. In addition, the patient is required to have castrate levels of testosterone (less than 50 ng/dL) and no radiographic evidence of metastatic disease.*' (17). Criteria for nmCRPC are generally consistent with the PCWG3 criteria – with the exception of European Association of Urology (EAU) guidelines which apply a more restrictive criteria for increase in PSA, with evidence of two consecutive PSA rises of >0.2 ng/ml considered suggestive of progression ((18)).

Figure 1: Schematic representation of disease evolution patterns to the clinical states of nonmetastatic castration-resistant prostate cancer (nmCRPC) (19)



Adapted from Mateo et al 2019 (19)

ADT=androgen deprivation therapy; BS=bone scintigraphy; CT=computerised tomography; HNPC=hormone-naïve prostate cancer; CRPC=castration-resistant prostate cancer;

mCRPC=metastatic castration-resistant prostate cancer; PC=prostate cancer; PSA=prostate specific antigen

It is estimated that 15% of new prostate cancer cases in the UK are CRPC, with 16% of these being non-metastatic (nmCRPC).

Management of nmCRPC

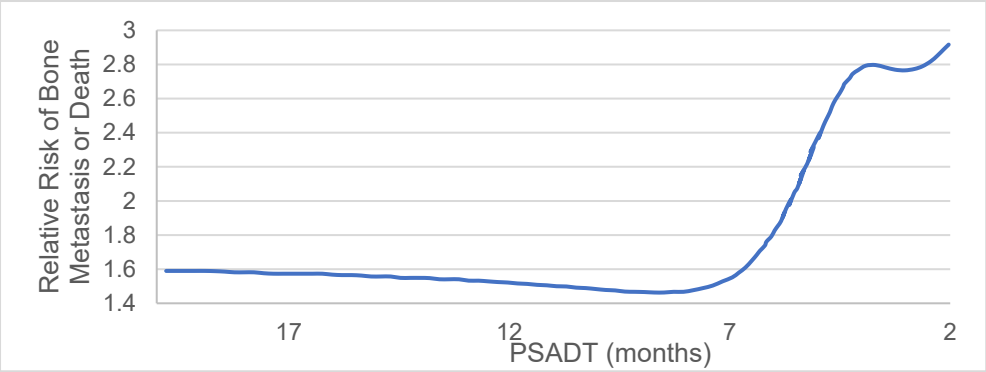
Patients with nmCRPC are generally asymptomatic but at risk for subsequent progression to metastatic disease with consequences of shortened survival, increased pain, reduced quality of life, increased healthcare costs and significant burden on the healthcare system (20). Approximately 30% of patients with nmCRPC will develop bone metastases within 2 years (21). The development of metastases has a significant, detrimental impact on the prognosis of men suffering with CRPC. This has recently been demonstrated in landmark analyses of the apalutamide SPARTAN trial, where metastasis development, regardless of time point, was associated with significantly greater risk of death in men with high-risk nmCRPC risk of death (adjusted Hazard ratio [HR] at 6 months for placebo / ADT treatment arm patients with metastases versus those without = 4.42; 95% CI, 2.14-9.17; P < .0001) (22). Given the morbidity and mortality associated with metastatic CRPC and the lack of definitive cure at this stage, delaying the development of metastases to bone and other sites in patients with nmCRPC is a key therapeutic goal, with a positive impact on patient quality of life (23-25).

In nmCRPC, androgen stimulation remains a major driver of progression to metastatic disease, and patients with nmCRPC are typically managed in the UK with continued ADT and active surveillance (18, 26, 27).

As highlighted above, all patients with nmCRPC are at risk of metastasis, but those considered to be at highest risk are those with a shorter PSA doubling time (PSADT) (i.e. ≤10 months) and increasing PSA levels and/or PSA velocity (i.e. the rate at which PSA increases (28-30) (see Figure 2). As such, increasing PSA levels and PSA kinetics can be used to identify high-risk nmCRPC patients – a strategy recommended in guidelines from the American Urological Association (AUA) (26),

EAU (18) and National Comprehensive Cancer Network (NCCN) (27), although there is no standard recommendation as to frequency of monitoring. The EAU suggests PSA testing every 3 months for asymptomatic men with nmCRPC (18). Patients with nmCRPC at high risk of metastases account for 40.29% of nmCRPC cases, resulting in 400-500 expected new cases of nmCRPC annually in England.

Figure 2: Risk of Bone Metastasis or Death According to PSADT



Adapted from: Smith et al. (2013). J Clin Oncol 31(30): 3800-3806 (29)

PSADT: Prostate-specific antigen doubling time.

Patients with nmCRPC had few treatment options until recently, when clinical results for the second generation androgen receptor inhibitors (ARIs) (enzalutamide, apalutamide) in high-risk nmCRPC demonstrated a significantly longer metastasis-free survival (MFS) when added to ADT, compared with patients treated with ADT alone (31, 32), (33). Apalutamide and enzalutamide are licenced for treatment of high-risk nmCRPC and the clinical evidence has prompted updates to several international guidelines (AUA), incorporating these new treatments into standard recommendations for high-risk nmCRPC patients (see Table 3). Enzalutamide was appraised by NICE (TA580; May 2019) and not recommended for treating high-risk hormone-relapsed non-metastatic prostate cancer. NICE appraisal of apalutamide in nmCRPC has been suspended until further notice.

In the UK, the current NICE guidelines (NG131 May 2019(33)) include the use of PSA levels and kinetics for active surveillance of men with localised prostate cancer (PSA monitoring every 3-4 months) but there is no specific guidance for the monitoring or treatment of patients with nmCRPC.

Table 3: Guideline Recommendations for nmCRPC Treatment

	ADT	Observation recommendations	Additional therapy
United Kingdom (UK)			
National Institute for Health and Care Excellence (NICE)			
NICE guideline 131 (NG131): Prostate cancer and diagnosis (May 2019)(33)	No nmCRPC-specific treatment recommendations, but guidelines for treatment and active surveillance of local and locally advanced disease		
Technology Appraisal (TA580) - Enzalutamide for hormone-relapsed non-metastatic prostate cancer	Enzalutamide is not recommended for treating high-risk hormone-relapsed non-metastatic prostate cancer. Cost-effectiveness estimates comparing enzalutamide plus androgen deprivation therapy with androgen deprivation therapy alone are uncertain and not within the range that NICE usually considers a cost-effective use of NHS resources.		
European			
European Association of Urology (EAU) (2019) (18)		PSA testing every 3 months for asymptomatic men.	Offer apalutamide or enzalutamide to patients with M0 CRPC and a high risk of developing metastasis (PSADT < 10 months) to prolong time to metastases (strong evidence).
United States (US)			
National Comprehensive Cancer Network (NCCN) v2.2019 (27)	Continue ADT to maintain castrate serum levels of testosterone < 50 ng/dL.	Observation with continued ADT especially if PSADT > 10 months.	Apalutamide or enzalutamide with continued ADT especially if PSADT ≤ 10 months (category 1 evidence). Secondary hormone therapy with continued ADT especially if PSADT ≤ 10 months.
American Urological Association (AUA) (2018) (26, 34)	Continue ADT.	Observation with continued ADT for high-risk patients who do not want or cannot have one of the standard therapies.	Apalutamide or enzalutamide with continued ADT for patients at high risk for developing metastatic disease (Standard, Evidence Level A). Second-generation androgen synthesis inhibitor

	ADT	Observation recommendations	Additional therapy
			(i.e. abiraterone + prednisone) to patients with nmCRPC at high risk for developing metastatic disease who don't want or can't have standard therapies and unwilling to accept observation (Evidence Level Grade C)
ADT=androgen deprivation therapy; nmCRPC=nonmetastatic castration-resistant prostate cancer; PSADT=prostate-specific antigen doubling time;			

Darolutamide

Darolutamide is a non-steroidal androgen receptor inhibitor (ARI) which significantly delays development of metastases in patients with nmCRPC (1).

Darolutamide is structurally distinct compared to the other ARIs, enzalutamide and apalutamide, consisting of two diastereomers, with a high binding affinity and selectivity to the androgen receptor. Its distinct structure, offers the potential for fewer and less severe toxic central nervous system (CNS)–related effects than apalutamide and enzalutamide, because of its low penetration of the blood brain barrier and low binding affinity for γ-aminobutyric acid type A ($GABA_A$) receptors, as shown in preclinical studies (4, 35) and demonstrated in the ARAMIS trial (1). Significant CNS toxicity was observed in the clinical trials for enzalutamide and apalutamide in the nmCRPC population, manifesting as seizures, falls, fractures, and, more commonly, fatigue, despite the fact that these trials excluded subjects with a history of seizure or any condition that might predispose a patient to a seizure. In addition, darolutamide was not associated with a higher incidence of hypertension than placebo in the ARAMIS study (1), whereas in the PROSPER and SPARTAN trials (31, 32), hypertension was more common among patients receiving enzalutamide or apalutamide than among those receiving placebo. An expert panel of UK Oncologists anticipate that clinicians may prefer to administer darolutamide over apalutamide and enzalutamide based on its more manageable adverse event

(AE) profile compared with apalutamide and enzalutamide (3). Patients with nmCRPC are largely asymptomatic, so it is critical that any treatments used to delay disease progression have minimal impact on daily activities and quality of life.

It is proposed that darolutamide would be used with ADT as first line treatment in patients with non-metastatic CRPC identified to be at high-risk of developing metastases through criteria based on international guidelines (i.e. increasing PSA levels and PSADT ≤ 10 months) (17, 18, 26, 27). These align with nmCRPC diagnostic criteria used in the ARAMIS clinical trial evaluating darolutamide (1). As suggested by experts (3), the use of darolutamide in this setting is expected to change the treatment patterns of other ARIs once patients progress to metastatic disease (see Figure 3: Current and proposed treatment pathway for patients with nmCRPC).

Figure 3: Current and proposed treatment pathway for patients with nmCRPC

	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%)

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

*in order of % of patients (highest to lowest)

^if bone metastases; after two lines of therapy or if patients are not eligible for any other treatment option

Source: Consensus of two workshop groups of an expert panel of UK Oncologists(3)

B.1.4. Equality considerations

No equality issues are anticipated.

B.2. Clinical effectiveness

B.2.1. Identification and selection of relevant studies

A systematic literature review (SLR) was developed to identify relevant studies for darolutamide in the treatment of nmCRPC. One clinical study was identified for the indication being appraised: a phase 3 randomised, double-blind, placebo-controlled study, ARAMIS (1). See appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to darolutamide in nmCRPC.

B.2.2. List of relevant clinical effectiveness evidence

Table 4: Clinical effectiveness evidence for darolutamide in high-risk nmCRPC (1, 36)

Study	ARAMIS (phase III). Also known as study 17712 and Orion study 3104007. Published as Fizazi (2019) (1).				
Study design	Multinational, randomised, double-blind, placebo-controlled, phase III efficacy and safety study.				
Population	Men with non-metastatic CRPC with high-risk of developing metastatic disease. These were patients with CRPC who had undetectable metastases by conventional imaging techniques (i.e. computed tomography, magnetic resonance imaging, bone scan).				
Intervention(s)	Darolutamide 600 mg (2 tablets of 300 mg) b.i.d. with food, equal to a daily dose of 1200 mg, Concurrently with ADT. n=955				
Comparator(s)	Placebo (2 tablets) b.i.d. with food. Concurrently with ADT. n=554				
	Yes	✓		Yes	✓

Company evidence submission template for darolutamide for treating non-metastatic hormone-relapsed prostate cancer [ID1443]

Indicate if trial supports application for marketing authorisation	No		**Indicate if trial used in the economic model**	No	
Rationale for use/non-use in the model	This trial provides the only RCT data on the clinical effectiveness of darolutamide when compared with standard therapy (i.e. ADT) in nmCRPC.				
Reported outcomes specified in the decision problem	**Metastasis-free survival (MFS)** **Time to prostate-specific antigen (PSA) progression** **Overall survival (OS)** **Adverse events (AE)** **Health related quality of life (HRQoL) – BPI-SF, EORTC-QLQ-PR25, FACT-P, EQ-5D-3L questionnaires**				
All other reported outcomes	Time to pain progression Time to initiation of first cytotoxic chemotherapy Progression-free survival (PFS) Time to initiation of subsequent antineoplastic therapy Percent of patients with PSA response **Time to treatment discontinuation** *Not reported in detail in this submission:* Time to first symptomatic skeletal event (SSE) Time to first prostate cancer-related invasive procedures Percent of patients with ECOG performance status deterioration Time to ECOG performance status deterioration Time to opioid use for cancer pain				
AE=adverse events; ADT=Androgen deprivation therapy; b.i.d.=Twice daily; BPI-SF=Brief Pain Inventory-Short Form questionnaire; CRPC=Castration-resistant prostate cancer; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQ-PR25= European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Prostate Cancer Module; EuroQol Group 5-dimension 3-level; FACT-P=Functional Assessment of Cancer Therapy-Prostate; HRQoL=health related quality of life; nmCRPC=non-metastatic castration-resistant prostate cancer; PSA=prostate-specific antigen; RCT=randomised controlled trial; SSE=symptomatic skeletal event;					

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

ARAMIS: A multinational, randomised, double-blind, placebo-controlled, phase 3 efficacy and safety study of darolutamide (ODM-201) in men with high-

risk non-metastatic castration-resistant prostate cancer (nmCRPC) [Study 17712; Orion study 3104007) (1, 36-40)

The primary objective of the ARAMIS study was to demonstrate the superiority of darolutamide combined with androgen deprivation therapy (ADT) in metastasis-free survival (MFS) when compared with placebo plus ADT in patients with nmCRPC. Efficacy analyses were based on independent blinded central imaging review.

Secondary objectives were to demonstrate the benefit of darolutamide for overall survival (OS), time to pain progression, time to initiation of first cytotoxic chemotherapy for prostate cancer, time to first symptomatic skeletal event (SSE), and to characterise the safety and tolerability of darolutamide.

Additional objectives of the study were to determine the benefit of darolutamide on progression-free survival (PFS), time to first prostate cancer-related invasive procedure, time to initiation of first subsequent antineoplastic therapy, the effect of darolutamide on prostate specific antigen (PSA) progression and PSA response, Eastern Cooperative Oncology Group (ECOG) performance status (PS) deterioration and health-related quality of life (HRQoL), and to evaluate the pharmacokinetic (PK) profile of darolutamide and keto-darolutamide exploring possible relationships between exposure and safety and efficacy response.

The primary completion of the study, evaluated when the target number of primary end point events (approximately 385), was reached on 3rd September 2018 (data cut-off date for the primary analysis). At the time there were 815 patients still on treatment, 615 in the darolutamide arm and 200 in the placebo arm. Results of this planned primary analysis were published in the New England Journal of Medicine in February 2019 (Fizazi 2019 (1)). Unpublished aspects of ARAMIS study results are drawn from the manufacturer licence application submission to the European Medicines Agency (EMA) (36, 37), the study Statistical analysis plan (SAP) (38), protocol (40) and clinical study report (CSR) (39). The results and analyses of all efficacy and safety outcomes are presented for events occurring up to the database cut-off date of 3rd September 2018.

Note: Patients in ARAMIS received androgen deprivation therapy (ADT) alongside their darolutamide or placebo treatment. Throughout this document, darolutamide + ADT treatment is referred to as 'darolutamide', and placebo + ADT treatment is referred to as 'placebo'.

Trial design and methodology (1, 36, 39)

The ARAMIS trial is an international, randomised, double-blind, placebo-controlled, phase 3 trial involving men with non-metastatic, castration-resistant prostate cancer and a prostate-specific antigen doubling time (PSADT) of 10 months or less. Patients had undetectable metastases by conventional imaging techniques (i.e. bone scan (BS), magnetic resonance imaging (MRI), computed tomography (CT)).

Settings and locations where the data were collected:

This multinational outpatient study took place across 409 study centres (hospitals, clinics or community practices) in 36 countries from:

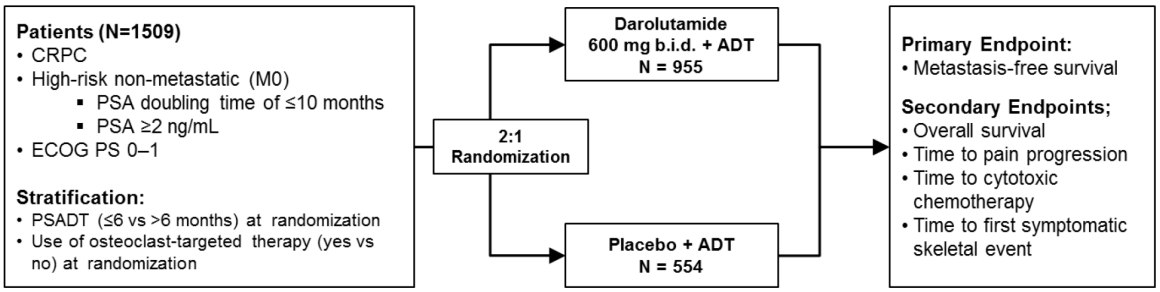
- North America (United States [US], Canada),
- Asia Pacific (Japan, South Korea, Taiwan),
- Rest of the World (ROW)
  - Europe (Austria, Belarus, Belgium, Bulgaria, Czech Republic, Estonia, Finland, France, Germany, Hungary, Italy, Latvia, Lithuania, Poland, Portugal, Romania, Russian Federation, Serbia, Slovakia, Spain, Sweden, Turkey, Ukraine, United Kingdom (UK)),
  - Middle East (Israel)
  - Africa (South Africa)
  - South America (Argentina, Brazil, Colombia, Peru)
  - Australia

12.2% of the randomised patients in ARAMIS were from North America (most of these [[redacted]%] from the US), [redacted]% were from the Asia Pacific, and [redacted]% were from the rest of the world (most from Europe, [redacted]%).

[redacted] clinical trial centres in the UK, randomised a total of [redacted] patients.

Study enrolment started in September 2014 and was completed in March 2018 during which time a total of 1509 patients had been randomised on a 2:1 ratio (955 in the darolutamide group and 554 in the matched placebo group). One patient in the darolutamide group (from the US) did not start treatment. Patients continued to receive androgen-deprivation therapy (luteinising hormone–releasing hormone [LHRH] agonist or antagonist) throughout the trial.

Figure 4: ARAMIS study design (36)



ADT=Androgen deprivation therapy; b.i.d.=Twice daily; CRPC=castration-resistant prostate cancer: ECOG PS=Eastern Cooperative Oncology Group performance status; N=total number of patients; CRPC=castration-resistant prostate cancer PSA=prostate specific antigen; PSADT=PSA doubling time;

Patients continued taking study therapy until protocol-defined progression (i.e. confirmed metastasis), discontinuation due to an adverse event (AE), or withdrawal of consent. Patients who initiated a prohibited therapy (listed in the protocol) before confirmation of metastasis had to discontinue the trial regimen and were followed for survival status.

After randomisation, patients were assessed at screening and at every subsequent visit until the end of the trial or death (i.e. days 1, 15, and 29; at 16 weeks; and at 16-week intervals thereafter) for vital signs, laboratory safety assessments, concomitant treatment and adverse events (AEs). Serum PSA level and pain (using the Brief Pain Inventory Short-Form [BPI-SF] questionnaire) and Disease assessments — including evaluation of ECOG performance status, bone scans, and CT and MRI of the chest, abdomen, and pelvis — were performed at screening, week 16, and every

subsequent 16-week visit. All scans were evaluated both locally and by blinded independent central review (1, 40).

Validated Health-related quality-of-life (HRQoL) instruments were assessed at screening, day 1, week 16, and the end of the treatment period including Functional Assessment of Cancer Therapy–Prostate (FACT-P), the prostate cancer–specific subscale of the FACT-P (FACT-P PCS), the generic EuroQol Group 5-dimension 3-level (EQ-5D-3L), and the European Organisation for Research and Treatment of Cancer quality of life questionnaire urinary symptoms subscale (EORTC-QLQ-PR25). FACT-P PCS and EORTC-QLQ-PR25 were also given every 16 weeks until the end of the trial or death.

All patients were followed with study visits every 16 weeks for the duration of the study irrespective of whether they had prematurely discontinued the study, were still receiving study treatments or whether metastasis had occurred (40).

An open-label part of the study, offering patients in the placebo arm the opportunity to benefit from darolutamide treatment, started officially on 30 OCT 2018 and was planned to continue until the cut-off date for the final OS analysis (15th November 2019). Patients in the darolutamide or placebo arms continuing open-label darolutamide treatment had study visits every 16 weeks until metastasis. After occurrence of metastasis, patients discontinued study treatment and were followed thereafter every 16 weeks for secondary and additional variables (40).

Method of randomisation

Randomisation was performed centrally, blocking by centre according to the design of the study, using a 2-step procedure. Firstly, a separate master randomisation schedule and study treatment package list was created using randomly permuted blocks. Secondly, randomly permuted blocks from the master randomisation schedule were assigned to the centres and study subjects using an interactive voice response system (IVRS), to receive either darolutamide or matching placebo using an allocation ratio 2:1, respectively. The study treatment package numbers were assigned to the unique subject number previously allocated by the investigator.

Randomisation was stratified according to PSA doubling time (≤6 months or >6 months) and the use of osteoclast-targeted therapy at randomisation (yes or no).

Study blinding

Alongside the darolutamide treatment group was a placebo treatment group in the ARAMIS study. Placebo tablets matched darolutamide tablets in packaging, size, shape and colour. Patients, investigators, study personnel and central review staff were blinded to treatment allocation using unique medication pack numbers assigned to the patient via the web-based randomisation (40). Also, the main efficacy analyses were based on independent blinded central imaging review. After completing the double-blind study phase the study was unblinded for the primary analyses.

Eligibility criteria

Unlike the trials for enzalutamide and apalutamide (31, 32), the ARAMIS trial permitted patients with previous seizure or conditions predisposing to seizure.

See Table 5.

Interventions

All ARAMIS patients received androgen deprivation therapy (ADT) (luteinising hormone–releasing hormone agonist [LHRH] or antagonist) throughout the trial.

Patients were randomly assigned in a 2:1 ratio in a double-blind manner to receive either:

- Oral darolutamide (600mg given as two 300mg tablets) twice daily with food (a daily dose of 1200 mg) or,
- matched oral placebo.

If considered necessary for patient's safety, the dose of study treatment could be reduced to 300 mg b.i.d.

The b.i.d. dosing was selected based on the half-life of darolutamide to ensure concentrations of darolutamide and its major metabolite at the target tissue during

the entire dosing interval that results in sufficient occupation of the androgen receptor.

Patients were instructed to take the tablets at about 12-hour intervals as close to the same time each day as possible, although subsequent pharmacokinetic data generated from the ARAMIS study indicates this is not necessary (36).

Patients continued taking study therapy until protocol-defined progression (i.e. confirmed metastasis), discontinuation due to an adverse event (AE), or withdrawal of consent.

Table 5: ARAMIS Inclusion and exclusion criteria (1)

Inclusion criteria	Exclusion criteria
1. Written informed consent given. 2. Males aged ≥18 years. 3. Histologically or cytologically confirmed adenocarcinoma of prostate without neuroendocrine differentiation or small cell features. 4. Castration-resistant prostate cancer (CRPC) defined as three rising prostate-specific antigen (PSA) levels after the nadir taken at least 1 week apart during androgen deprivation therapy (ADT). If the patient has a history of antiandrogen use, the most recent PSA value must be obtained at least 4 weeks after anti-androgen withdrawal. 5. Castrate level of serum testosterone (<1.7 nmol/l [50 ng/dl]) on gonadotrophin-releasing hormone (GnRH) agonist or antagonist therapy or after bilateral orchidectomy at screening or Day 1 visit. Patients who have not undergone bilateral orchidectomy must continue GnRH therapy during the study. 6. PSA doubling time (PSADT) of ≤10 months and PSA ≥2 ng/ml at screening. 7. Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. 8. Blood counts at screening: haemoglobin ≥9.0 g/dl, absolute neutrophil count ≥1500/µl (1.5×109/l), platelet count ≥100,000/µl (100×109/l) (patient must not have received	1. History of radiographically documented metastatic disease at any time or presence of detectable metastases by blinded central reading within 42 days prior to start of study treatment. Presence of pelvic lymph nodes <2 cm in short axis below the aortic bifurcation is allowed. 2. Symptomatic local-regional disease that requires medical intervention including moderate/severe urinary obstruction or hydronephrosis due to prostate cancer. 3. Acute toxicities of prior treatments and procedures not resolved to grade ≤1 or baseline before randomisation. 4. Prior treatment with: (1) second-generation androgen receptor (AR) antagonists such as enzalutamide and apalutamide, or darolutamide or other investigational AR antagonists; (2) CYP17 enzyme inhibitors, such as abiraterone acetate, TAK-700; or (3) oral ketoconazole for longer than 28 days. 5. Use of oestrogens or 5-α reductase inhibitors (finasteride, dutasteride) within 28 days before randomisation and AR antagonists (bicalutamide, flutamide, nilutamide, cyproterone acetate) at least 28 days before screening. 6. Prior chemotherapy or immunotherapy for prostate cancer, except adjuvant/neoadjuvant treatment completed >2 years before randomisation. 7. Use of systemic corticosteroid with dose greater than the equivalent 10 mg of prednisone/day within 28 days before randomisation. 8. Radiation therapy (external beam radiation therapy [EBRT], brachytherapy, or radiopharmaceuticals) within 12 weeks before randomisation. 9. Severe or uncontrolled concurrent disease, infection or comorbidity that, in the opinion of the investigator, would make the patient inappropriate for enrolment. 10. Treatment with an osteoclast-targeted therapy (bisphosphonate or denosumab) to prevent skeletal-related events within 12 weeks before randomisation. Patients receiving osteoclast-targeted therapy to prevent bone loss at a dose and schedule indicated for osteoporosis may continue treatment at the same dose and schedule. 11. Known hypersensitivity to the study treatment or any of its ingredients.

any growth factor or blood transfusion within 7 days of the haematology laboratory obtained at screening). 9. Screening values of serum alanine transaminase (ALT) and aspartate transaminase (AST) ≤2.5 x upper limit of normal (ULN), total bilirubin ≤1.5 x ULN (except patients with a diagnosis of Gilbert's disease), creatinine ≤2.0 x ULN. 10. Sexually active patients, unless surgically sterile, must agree to use condoms as an effective barrier method and refrain from sperm donation during the study treatment and for 3 months after the end of the study treatment.	12. Major surgery within 28 days before randomisation. 13. Any of the following within 6 months before randomisation: stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft; congestive heart failure New York Heart Association (NYHA) Class III or IV. 14. Uncontrolled hypertension as indicated by a systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg at screening. 15. Prior malignancy. Adequately treated basal cell or squamous cell carcinoma of skin or superficial bladder cancer that has not spread behind the connective tissue layer (i.e., pTis, pTa, and pT1) is allowed, as well as any other cancer for which treatment has been completed ≤5 years ago and from which the patient has been disease-free. 16. Gastrointestinal disorder or procedure that expects to interfere significantly with absorption of study treatment. 17. Active viral hepatitis, active human immunodeficiency virus (HIV), or chronic liver disease. 18. Treatment with any investigational drug within 28 days before randomisation. 19. Any condition that, in the opinion of the investigator, would impair the patient's ability to comply with the study procedures. 20. Unable to swallow study medications and comply with study requirements.

Missed tablets

If a dose of darolutamide was missed the dose could be taken as soon as the patient remembers it prior to the next scheduled dose. If the patient remembers only at the time of the next scheduled dose, only one 600 mg dose should be taken and not more due to the absorption limitation (36).

Treatment compliance (1, 39)

Reasons for any non-compliance to the treatment regimen defined in the protocol were documented. Drug accountability records were kept by each investigator, including details of the date and amount of study drug received by each patient, a drug dispensing list, and drugs accidentally or deliberately destroyed (39).

All remaining study drugs and study drug containers were returned to the study centre at the start of open-label treatment visit and at the end-of-study treatment visit. Study drug tablets not returned were considered to have been taken unless otherwise specified. At the end of the study, any remaining drugs were collected and returned to the sponsor. Any discrepancies between the returned and expected returned study drugs were explained.

As of the cut-off date (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).

Treatment compliance was high in both treatment arms; the mean percent of planned dose taken was [redacted] in the darolutamide + ADT arm (median [redacted]) and [redacted] in the placebo arm (median [redacted] %). The median time under treatment (including dose interruptions/delays) was 14.80 months (<0.1-44.3 months) in the darolutamide + ADT arm, and 11.04 months (0.1-40.5 months) for patients in the placebo arm, and at the time of database cut-off, 64% of darolutamide + ADT patients and 36% of the placebo group were still receiving the assigned trial regimen.

Permitted and disallowed concomitant medications (39, 40)

The taking of concomitant medications was balanced between the two treatment arms. In the darolutamide + ADT treatment group, [redacted] patients ([redacted]) took at least one concomitant medication (n=[redacted] [redacted] placebo group).

Overall, the most common concomitant medications (i.e. those reported for more than half of patients in either arm) were endocrine therapy ([redacted] vs. [redacted] of patients), agents acting on the renin-angiotensin system ([redacted] vs. [redacted]), and analgesics ([redacted] vs. [redacted]) in the darolutamide + ADT arm and in the placebo arm, respectively.

Per protocol, the use of osteoclast-targeted therapy was allowed for the treatment of osteoporosis and was reported for [redacted] and [redacted] of patients at randomisation, for darolutamide and placebo patients respectively (39). Osteoclast therapy was a stratification factor during randomisation.

The following medications were disallowed: Any investigational medicinal product, Radiopharmaceuticals, Immunotherapy (e.g. sipuleucel-T), Cytotoxic chemotherapy and any other systemic antineoplastic therapy, Enzalutamide, ARN-509, bicalutamide, flutamide, nilutamide, Cyproterone acetate, oestrogen, 5 α-reductase inhibitor, Abiraterone acetate, TAK-700 or other CYP17 inhibitors, Systemic ketoconazole (as antineoplastic therapy), Osteoclast-targeted therapy such as bisphosphonate or denosumab [Patients receiving treatment with osteoclast-targeted therapy at a dose and schedule indicated for osteoporosis prior to study entry may continue treatment at the same dose and schedule.], Continuous use of systemic corticosteroid with dose greater than the equivalent 10 mg of prednisone/prednisolone per day. Short-term use of systemic corticosteroids with higher doses up to 28 days during the study treatment period was allowed, but treatment was kept as short as possible.

Patients who took a prohibited therapy (listed in the protocol) before confirmation of metastasis had to discontinue the trial regimen and were followed for survival status - 17 patients (1.8%) in the darolutamide + ADT treatment arm and 25 (4.5%) patients receiving placebo discontinued study treatment due to receiving prohibited concomitant treatment.

Efficacy outcome measures in ARAMIS

The primary efficacy outcome in ARAMIS was metastasis-free survival (MFS), defined as the time from randomisation to confirmed evidence of distant metastasis on imaging or death from any cause, whichever occurred first.

MFS was selected on the basis that the transition from nmCRPC to detectable metastatic disease is a clinically relevant event that can be associated with multiple symptoms and illness and result in the need for additional interventions. This was determined in 2011 at a US Food and Drug Administration (FDA) Oncologic Drugs Advisory Committee (ODAC) meeting which discussed clinical trial endpoints and trial designs that might be used to support drug approval in nmCRPC. The endorsement of MFS as a reasonable endpoint included the requirement that the clinical benefit of a drug would provide a substantial magnitude of improvement on MFS and a favourable safety profile (41). A group of expert UK oncologists who treat prostate cancer also agreed that MFS is a meaningful endpoint both clinically and to patients in the treatment of prostate cancer (3).

Table 6 summarises all relevant ARAMIS study endpoints, including details of when / how each were measured.

All endpoints described were pre-specified in the analyses and were appropriate measures for this event-driven trial. All evaluations were in accordance with Good Clinical Practice (GCP) to ensure safety of patients participating in research.

Table 6: Relevant endpoints and measures in ARAMIS (37)

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

Endpoint	Definition & timing of assessment / measure
	non-osseous tissue was defined as new distant pathologic lymph nodes or other pathological lesion according to RECIST 1.1 (42). 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 cutoff 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 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

Endpoint	Definition & timing of assessment / measure
	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 to PSA progression	Time from randomisation to the date of first PSA progression. Defined in accordance with Prostate Cancer Working Group 2 (PCWG2) criteria (43). 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 (43). 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

Endpoint	Definition & timing of assessment / measure
	performance 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.

Endpoint	Definition & timing of assessment / measure
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.
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	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.
Percent of patients with improvement of EORTC-QLQ-PR25 urinary symptoms	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 to worsening of EORTC-QLQ-PR25 urinary symptom score	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.

Endpoint	Definition & timing of assessment / measure
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 on a vertical graduated visual analog scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).
Percent of patients with deterioration of EQ-5D-3L utility index score at 16 weeks	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;

Table 7: PCWG2 criteria for PSA progression (1)

Patient category	PCWG2 criteria for progression
Decline from baseline at week 16	≥25% increase in PSA and increase in absolute PSA levels of ≥2 ng/ml above the nadir, confirmed by a second consecutive value obtained 3 or more weeks later
No decline from baseline at week 16	≥25% increase in PSA and increase in absolute PSA levels of ≥2 ng/ml above baseline confirmed by a second consecutive value obtained 3 or more weeks later
PCWG2=Prostate Cancer Working Group 2; PSA=prostate specific antigen. Note: Early increases in PSA values before the 16 weeks were not considered as PSA progression	

See section B.2.7 and Appendix E for details of pre-planned subgroup analyses.

Patient Baseline characteristics

Patient demographic and disease characteristics were similar across the two treatment groups (see Table 8) (1, 37, 39).

The median age of patients in ARAMIS was 74.0 years in both treatment arms, with most patients in the [redacted] and [redacted] age categories. Race was described as White in most patients ([redacted]%), followed by Asian ([redacted]%) and Black or African American ([redacted]%). Of all randomised patients, [redacted]% were from North America, [redacted]% from Asia Pacific and [redacted]% of patients from the rest of the world (ROW), of which [redacted]% were from Europe. The North America population consisted mostly of patients from the US ([redacted]% of randomised patients from North America).

Most patients ([redacted]) were in the BMI categories above [redacted] kg/m2. At baseline, most patients had normal ([redacted]) or mildly impaired ([redacted]) renal function, and normal hepatic function ([redacted]).

Randomisation was stratified according to PSADT (≤6 months vs. >6 months) and use of osteoclast-targeted therapy (allowed for treatment of osteoporosis per protocol; yes vs. no). Median PSADT was 4.4 months in the darolutamide + ADT arm and 4.7 months in the placebo arm, with most patients having PSADT of ≤6 months. Use of osteoclast therapy was reported for 3.8% (darolutamide + ADT arm) and 5.1% (placebo arm) patients at randomisation.

Tumour stage at initial diagnosis was most commonly in the T3 stage group (Darolutamide + ADT arm [redacted]%; placebo arm [redacted]%) and most patients had an ECOG performance status at baseline of 0, and a Gleason score [redacted]. The study protocol allowed presence of regional pathological lymph nodes (i.e. Presence of pelvic lymph nodes < 2 cm in short axis below the aortic bifurcation); however, the majority of patients had no baseline regional pathological lymph nodes by central imaging review. During the efficacy review, performed by a separate group of independent central imaging reviewers, all images were assessed, including baseline images. There were 5.2% (n=50) of patients in the darolutamide arm and 7.0% (n=39) of patients in the placebo arm who were retrospectively classified with metastases at baseline (39).

The median time since initial prostate cancer diagnosis to start of study treatment was 86.2 vs. 84.2 months (darolutamide + ADT vs. placebo). Median PSADT and median PSA values at baseline were similar between the treatment arms. The median time since becoming castration-resistant to the start of study treatment was similar in the treatment arms (darolutamide + ADT: [redacted] months [redacted]; placebo: [redacted] months [redacted]), with a mean of approximately [redacted] months in both arms.

Most patients (1508/1509) reported a prior procedure for primary treatment for prostate cancer. The most common primary therapeutic procedures / treatments for prostate cancer were chemical castration (darolutamide + ADT [redacted] vs. placebo [redacted]), prostatectomy ([redacted] vs. [redacted], respectively), radiotherapy ([redacted] vs. [redacted], respectively) and orchidectomy ([redacted] vs. [redacted], respectively) (37).

Overall, the use of prior hormonal therapy and / or orchidectomy to maintain castrate levels of testosterone was similar between treatment arms. 96% patients in both

treatment arms received prior anti-cancer medications for prostate cancer. Most patients had ≥ 2 prior hormonal therapies (76% in both treatment arms). Common previous hormonal therapies for prostate cancer (received by ≥10% of all patients) included leuprolide ([redacted] vs [redacted]%), goserelin ([redacted]% vs. [redacted]%), triptorelin ([redacted] vs. [redacted]%), bicalutamide ([redacted]% vs. [redacted]%), flutamide ([redacted]% vs. [redacted]%), and cyproterone ([redacted]% vs. [redacted]%)

Table 8: Baseline demographic and disease characteristics for the ARAMIS study population (1, 37, 39)

	Darolutamide +ADT N=955	**Placebo 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)

	Darolutamide +ADT N=955	Placebo N=554
> 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;

[a] Race was not collected if ethnicity was documented as 'Hispanic or Latino'. Data collection for race and ethnicity was not permitted in some countries e.g. France.

[b] Predominantly includes European countries (15% of patients came from non-European countries).

[c] Testosterone levels from screening or day 1 could be used for eligibility, and all patients met the inclusion criterion of having testosterone level lower than 1.7 nmol per litre

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Analysis sets

The primary population for efficacy analysis was the Intention-to-treat (ITT) analysis set, also termed the full analysis set (FAS), which includes all unique randomised patients.

The population for safety analysis consisted of all patients who received at least one dose of study treatment.

Table 9: Definition of relevant data analysis sets in ARAMIS

Analysis set	**Definition**	**Number of valid patients in treatment group**		
		Darolutamide + ADT	**Placebo**	**TOTAL**
Intention-to-treat (ITT) [Full analysis set (FAS)]	All randomised patients.	N=955 (100%)	N=554 (100%)	N=1509
Safety analysis set (SAF)	All randomised patients who received at least one dose of study medication.	N=954 (99.9%)	N=554 (100%)	N=1508
	Excluded as did not receive study medication	1 (0.1%)	0	N=1

Overview of statistical analyses

Table 10: Summary of statistical analyses in ARAMIS (1, 37, 38)

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
ARAMIS	A survival distribution function was used as a basis for the statistical hypothesis. The hypothesis was two-sided, although superiority over placebo was anticipated: H_0: $S_{DAROLUTAMIDE}(t) = S_{PBO}(t)$, for all $t > 0$ H_1: $S_{DAROLUTAMIDE}(t) \neq S_{PBO}(t)$, for some $t > 0$ Where S(t) represents estimated survival distribution at time t for MFS.	**Primary efficacy analysis:** The cut-off date for the primary analyses was 3rd September 2018, Conducted when 437 MFS events had occurred. Data from patients without events were censored at the last assessment date. Kaplan–Meier curves, including median survival times and their 95% CIs, were calculated; the hazard ratio was calculated with a Cox proportional-hazards model. A two-sided overall alpha of 0.05 was used for the efficacy analysis of MFS. The primary MFS analysis was performed considering baseline metastases as events at the randomisation date (non-censored analysis). During the blinded central imaging review (where all scans were reviewed again) some patients were classified with metastases already at baseline. An additional MFS analysis was performed censoring baseline metastases at randomisation (censored analysis). The primary analysis and all sensitivity analyses were stratified by information collected in the IVRS, except for one sensitivity analysis stratified with information from CRFs, which is considered in case of discrepancies with IVRS clinically more verifiable as it could be queried and confirmed. Randomisation stratification factors were used to adjust analyses of the primary and all secondary efficacy end points. **Secondary & tertiary efficacy analyses:** For the secondary efficacy variables, the analysis done at the time of the MFS analysis was considered an interim analysis. A final analysis for OS and other secondary end points was planned for when the predetermined number of overall survival OS events (~240) had occurred. The cut-off date for	The sample size of 1500 (randomly assigned in a 2:1 ratio to receive darolutamide or placebo) was calculated based on the primary end point, metastasis-free survival, assuming a hazard ratio of 0.71 for death or metastasis in the darolutamide group. A sample of 1500 patients with approximately 385 primary end-point events provided the trial with 91% power to detect a significant difference in metastasis-free survival with the use of a log-rank test at a two-sided significance level of 0.05. Other assumptions included median MFS for placebo: 25 months, 40 months accrual time	**Handling of missing data:** Incomplete dates of events (e.g. missing day of the month) were imputed as the earliest possible dates. Patients with missing event dates (e.g. due to withdrawal of consent, lost to follow up or not known to have died at the analysis cut-off date) were censored. **Missing patient-reported outcome data -** subscale scores were prorated where there were missing responses for one or more items: - FACT-P: done by multiplying the sum of the subscale by the number of items in the scale, then dividing the number of items actually answered. Prorating of scores was acceptable as long as >50% of the items were answered (assuming that the score of missing items was similar to those of non-missing items). If ≤50% of the items were answered for any domain, then the score of that domain was set to missing. The total score was then calculated as the sum of the un-weighted subscale scores.

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		final OS analysis was 15th November 2019 and results will be presented in due course. Secondary and exploratory end points were analysed with the same methods as the primary end point, except for the percentage of patients with PSA response and percentage of patients with deterioration in ECOG performance status, which were analysed with the Cochran–Mantel–Haenszel test. Secondary end points were evaluated in a hierarchical order and only if the primary endpoint was significant: (1) OS (2) time to pain progression (3) time to initiation of first cytotoxic chemotherapy for prostate cancer (4) time to first SSE. An alpha spending function was used for the sequential testing, with the overall alpha (significance level of 0.05) split between the primary analysis and final analysis. The end point of OS was used to determine the alpha spend and significance threshold for each of the secondary end points. For the interim analysis of OS, a predefined alpha of 0.0005 was used. For QoL variables, an ANCOVA model was used to compare the time-adjusted AUC between groups, with covariates for baseline scores and randomisation stratification factors. The least-squares mean and 95% CI was estimated for each group and for the difference between the groups. Statistical analysis and generation of patient data listings were performed with the use of SAS for Windows, version 9.2 (SAS Institute).	and a dropout rate of 40%.	The FACT-P total score was set to missing if the related overall item response rate was less than or equal to 80%. -EQ-5D-3L: if there was a missing or ambiguous answer (i.e. marking of more than one answer) on the five-dimension questions, then the index score was considered missing. -BPI-SF: two scores were derived: one for the pain severity score, where if one answer was missing then the score was set to 'missing'; and one for the pain interference score, where if four or more answers out of the seven questions were missing then the score was set to 'missing'. -EORTC-QLQ-PR25: six scales were created. If ≤50% of the items were answered for any of the scales, then the score of that scale was set to 'missing'. **Handling of dropouts:** Patients withdrawn from study treatment were not replaced.
ANCOVA=analysis of covariance; AUC=area under the curve; BPI-SF=Brief Pain Inventory–Short Form; CI=confidence interval; CRF=case report form; EQ-5D-3L= EuroQol 5-dimensions 3-levels; FACT-P= Functional Assessment of Cancer Therapy-Prostate; MFS=metastasis-free survival; IVRS=interactive voice reporting system; QoL=quality of life; SSE= symptomatic skeletal event;				

Sensitivity analysis of primary end point (38)

The following sensitivity analyses were performed for MFS:

1) censoring patients who died before documented metastasis

2) considering all prohibited new anticancer treatment that started prior to documented metastasis as an event

3) using stratification data from the CRF

4) without including stratification factors in the model

5) using MFS data based on investigator assessment

6) considering all deaths independent of time of occurrence as MFS events

7) using the event at the date of the first post-baseline scan with metastasis instead of event at randomisation, for patients with baseline metastasis. If no metastasis was documented in post baseline scans, the patient was censored at the last available scan date. In case the patient did not have any post-baseline scans, the patient was censored at randomisation.

8) excluding patients with the primary reason for permanent discontinuation of study treatment of “judgment of investigator” or “personal reason”, and without MFS events (post-hoc analysis).

Sensitivity analyses 1-7 were also performed for MFS with baseline metastasis censored at randomisation date.

Post-hoc analyses

Additional post-hoc analyses included (37):

[redacted]

[redacted]F

or information on subgroup analyses, see section 2.7.

See Appendix D1.2 for 'Participant flow in the ARAMIS study'.

B.2.5. Quality assessment of the relevant clinical effectiveness evidence

Table 11 presents a quality assessment of the ARAMIS study. ARAMIS was completed to the highest standard with adequate randomisation and blinding procedures. Please see Appendix D1.3 for a detailed quality assessment.

Table 11. Quality assessment results for ARAMIS

Trial number (acronym)	**ARAMIS study**
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes / Yes / Yes
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination'	

The ARAMIS study reflects clinical practice in England for the following reasons:

- Current management of high risk nmCRPC patients in the UK relies largely on the continuation of ADT, hence ADT as the comparator in ARAMIS is congruent with routine clinical practice in England.
- Darolutamide is not yet licensed for use in the UK in high-risk nmCRPC, however, when it becomes available it will be prescribed and used in the same way as in the ARAMIS study (e.g. dose and administration, indication).
- Subgroup analyses in ARAMIS were consistent with the overall study results, including consistency across regions. This suggests that the study population, and hence the efficacy and safety results would be generalisable to the population found in clinical practice in England.
- An advisory panel of UK Oncologists agreed that the baseline characteristics of the patients in ARAMIS largely reflect UK clinical practice (3).

B.2.6. Clinical effectiveness results of the relevant trials

Notes

1) The results and analyses of all efficacy and safety outcomes presented in this submission are based on the primary efficacy analysis database cut-off of 3rd September 2018.

2) All patients entering the study had been assessed as having no metastases in the blinded independent eligibility review of radiological images. However, as part of the blinded central imaging review for the efficacy assessment to determine metastases, all scans, including the baseline scans, were reviewed again. The blinded central imaging review for efficacy was performed by a pool of radiologists separate from those who performed the blinded central imaging review for eligibility. During the central efficacy imaging review, which included the baseline scans, some patients were retrospectively classified as having metastases at baseline (50/955 [5.2%] darolutamide patients and 39/554 [7.0%] placebo patients). These patients were included in the primary analysis of metastasis-free survival, counted as events at baseline randomisation date.

Summary of efficacy results

The phase III, international, placebo-controlled, double-blind, multicentre study ARAMIS randomised 1509 patients on a 2:1 ratio to receive study treatment (darolutamide n=955; placebo n=554). The study demonstrated the superiority of

darolutamide (combined with androgen deprivation therapy) over androgen deprivation therapy alone in improving metastasis-free survival in patients with nmCRPC who are at high risk for developing metastases.

ARAMIS met its primary efficacy objective, with darolutamide treatment providing a statistically significant improvement in MFS compared to placebo. Median MFS was 40.4 months in the darolutamide arm compared with 18.4 months in the placebo arm (HR=0.41; 95% CI, 0.34 to 0.50), signifying superiority of darolutamide and a 59% reduction in the risk of metastasis or death (p<0.001).

The secondary endpoints were tested with a hierarchical gatekeeping procedure, with overall survival (OS) to be analysed first. At the time of the primary analysis data cut-off (3rd September 2018), 136 out of the 240 OS events planned for the final OS analysis had occurred. Median OS was not reached in either treatment arm (HR=0.71; 95% CI, 0.50 to 0.99; p=0.045), however, a positive trend in the improvement of survival for patients treated with darolutamide was observed. *Note: The final OS analysis data cut-off has now been reached (15th November 2019) and there is a significant difference in OS favouring patients receiving darolutamide. These results will be supplied to NICE as soon as they are available.*

Subgroup analyses of MFS and OS were consistent with and supportive of the main analyses, as were sensitivity analyses of MFS.

A significant benefit in favour of darolutamide compared to placebo was also observed for the other secondary endpoints time to pain progression (Median time: 40.3 months Darolutamide vs. 25.4 months placebo; HR=0.65; 95% CI, 0.53 to 0.79), time to initiation of first cytotoxic chemotherapy (HR=0.43; 95% CI, 0.31 to 0.60), and time to first SSE (HR=0.43; 95% CI,0.22, 0.84]). Results of analyses of all additional endpoints including PFS (median PFS times of 36.8 months and 14.8 months; HR= 0.38; 95% CI, 0.33 to 0.45; p<0.001), time to initiation of subsequent antineoplastic therapy, time to PSA progression (median times of 33.2 months and 7.3 months; HR= 0.13; 95% CI, 0.11 to 0.16; p<0.001), and PSA response rate further supported the conclusion of clinical benefit of darolutamide over placebo. Analysis of completed BPI-SF, FACT-P, EORTC-QLQ-PR25, and EQ-5D-3L questionnaires confirmed that HRQoL was maintained during treatment with

darolutamide. Darolutamide did not adversely affect urinary symptoms as measured by EORTC-QLQ-PR25 over the duration of therapy compared to placebo. Safety analyses showed darolutamide treatment to be well tolerated, with no meaningful differences compared to the placebo arm (including falls, fractures, seizures, cognitive disorders, and hypertension), and adverse events (AEs) representative of the underlying disease and age of the patient population.

Overall, the ARAMIS study provides evidence of darolutamide being a highly effective treatment option for nmCRPC patients with strong MFS benefit supported by the secondary (OS, time to pain progression, time to cytotoxic chemotherapy and time to first SSE) and additional efficacy endpoints.

Primary Efficacy Outcome

Metastasis-free survival (MFS)

The planned primary analysis was performed after 437 primary end-point events had occurred. The ARAMIS study met its primary endpoint with a median MFS of 40.4 months (95% confidence interval [CI]: [34.33; NR]) with darolutamide + ADT, as compared with 18.4 months (95% CI: [15.5; 22.3]) with placebo. Thus, superiority of darolutamide over placebo with respect to MFS was shown with a hazard ratio [HR] of 0.41 (95% CI, 0.34 - 0.50; P<0.001), representing a 58.7% reduction in the risk of metastases or death. For the primary analysis, patients with baseline metastasis by central efficacy imaging review were non-censored, i.e. counted as events at the randomisation date). In both treatment arms most reported metastases were located in [redacted].

Overall, 18.6% (41/221) of the MFS events in the darolutamide + ADT arm were deaths, compared to 8.8% (19/216) of MFS events in the placebo arm.

[redacted]

[redacted]

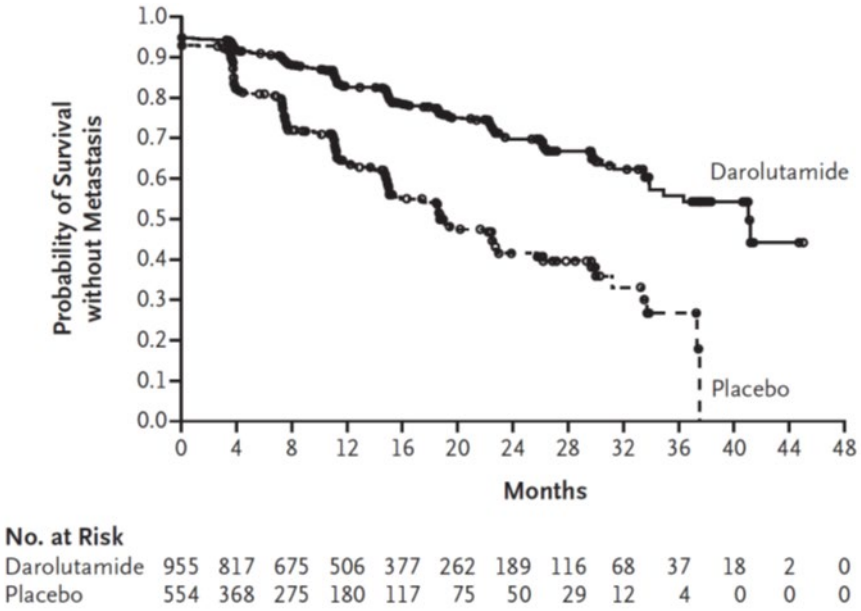
The event-free rates at 4, 8, 12, 24 and 36 months demonstrate that the benefit of darolutamide treatment with regard to MFS was maintained over time.

Table 12: Metastasis-free survival in the ARAMIS study (FAS; with baseline metastases non-censored) (1, 36)

	Darolutamide + ADT N=955	**Placebo N=554**
Number (%) of patients with event	221 (23.1%)	216 (39.0%)
Number (%) of patients censored [a]	734 (76.9%)	338 (61.0%)
MFS (months)		
Median [95% CI]	40.4 [34.3, NR]	18.4 [15.5, 22.3]
Range (without censored values)	[redacted]	[redacted]
Range (including censored values)	[redacted]	[redacted]
4-month event-free rate [95% CI]	[redacted]	[redacted]
8-month event-free rate [95% CI]	[redacted]	[redacted]
12-month event-free rate [95% CI]	[redacted]	[redacted]
24-month event-free rate [95% CI]	[redacted]	[redacted]
36-month event-free rate [95% CI]	[redacted]	[redacted]
48-month event-free rate [95% CI]	[redacted]	[redacted]
HR: (Darolutamide + ADT/ Placebo) [95% CI] [b]	0.41 [0.34, 0.50]	
Two-sided p-value from log rank test	<0.001	
CI=confidence interval; FAS=full analysis set; HR=hazard ratio; IVRS=interactive voice response system; MFS=metastasis-free survival; NR=not reached / value cannot be estimated; ** censored observation		

	Darolutamide + ADT N=955	Placebo N=554
[a] patients with documented metastases at baseline were considered to have an MFS event at randomisation [b] 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 (IVRS stratification)		

Figure 5: Kaplan Meier Analysis of Metastasis-free survival (1)



Additional and Sensitivity Analyses of primary endpoint

When censored for baseline metastases, MFS results were consistent with results of the non-censored analysis – median MFS for darolutamide treatment group 40.51 months vs placebo treatment group 22.08 months (HR = 0.356; 95% CI, 0.287 to 0.441; p<0.000001) (37).

Results of all sensitivity analyses supported the results of the primary MFS analysis with all except one analysis resulting in lower HR (see Table 12). The slightly higher HR for the non-stratified analysis (HR=0.42; P<0.001) is a technical consequence of omitting the stratification factors in the analysis.

MFS sensitivity analyses 1-7 were also performed with baseline metastasis censored at randomisation date and results were consistent with the sensitivity analyses of MFS with baseline metastasis non-censored.

Consistent MFS benefit for darolutamide was also demonstrated for all subgroups analysed (see Appendix E).

Table 13: Sensitivity analyses of MFS with baseline metastasis non-censored (FAS)

Sensitivity analysis		Hazard ratio: Darolutamide / Placebo [95% CI] [a]	Two-sided p-value from log-rank test
Analysis 1	Censoring of patients who died before documented metastasis	0.374 [0.304, 0.459]	<0.000001
Analysis 2	Considering all prohibited new anti-cancer treatment that started prior to documented metastasis as event	0.346 [0.293, 0.409]	<0.000001
Analysis 3 [b]	Using stratification data from the CRF	0.407 [0.336, 0.493]	<0.000001
Analysis 4 [b]	Without including stratification factors in the model	0.417 [0.345, 0.504]	<0.000001
Analysis 5	Using MFS data based on investigator assessment	0.399 [0.337, 0.473]	<0.000001
Analysis 6	Considering all deaths independent of the time of occurrence as MFS events	0.411 [0.341, 0.495]	<0.000001
Analysis 7	Using the event at the date of the first post-baseline scan with metastasis instead of the event at randomisation, for patients with baseline metastasis. If no metastasis was documented in post-baseline scans, the patient was censored at the last available scan date. In case the patient did not have any post-baseline scans, the event would remain at	0.391 [0.323, 0.474]	<0.000001

Sensitivity analysis		Hazard ratio: Darolutamide / Placebo [95% CI] [a]	Two-sided p-value from log-rank test
	baseline and the patient was censored at randomisation.		
Analysis 8 [c] (post-hoc)	Excluding patients with the primary reason for permanent discontinuation of study treatment of 'judgment of investigator' or 'personal reason', and without MFS events.	0.375 [0.310, 0.453]	<0.000001

CI=confidence interval; CRF=case report form; FAS=full analysis set; MFS=metastasis-free survival

[a]: A hazard ratio <1 indicates superiority of darolutamide over placebo. The hazard ratio and its 95% CI were based on Cox Regression Model.

b: Descriptive statistics results and Kaplan-Meier curves for sensitivity analysis 3 (using stratification

data from the CRF) and sensitivity analysis 4 (without including stratification factors in the model) were the same as in the main analysis.

c: Post-hoc sensitivity analysis 8 excluded patients without an MFS event who permanently discontinued treatment with the primary reason being 'judgment of the investigator' (2.4% in the darolutamide arm, 9.2% in the placebo arm) or 'personal reason' (5.5% in the darolutamide arm, 10.8% in the placebo arm)

Table 14: Summary of results from the ARAMIS study (FAS) (1, 37)

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						
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
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	NR	48 (5.0%)	NR	70 (12.6%)	0.33 [0.23-0.47]	<0.001
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;						

Secondary Efficacy Outcomes

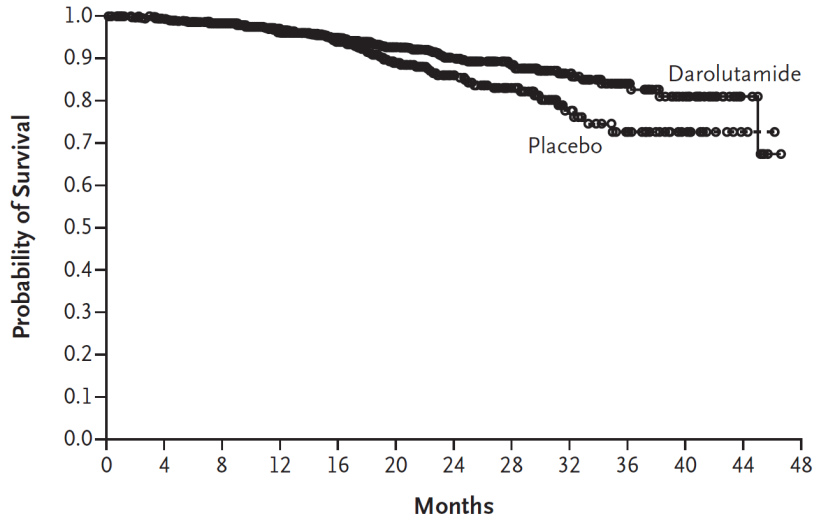
Secondary endpoints were analysed in the FAS and were tested with a hierarchical gatekeeping procedure outlined in Table 14. For all secondary end points, darolutamide was associated with greater benefits than placebo (Table 14).

Overall survival (OS)

At the time of the data cut-off for the primary analysis (3rd September 2018), 136 out of the 240 OS events planned for the final OS analysis had occurred: 78 in the darolutamide group and 58 in the placebo group. Darolutamide was associated with a lower risk of death than placebo (hazard ratio for death, 0.71; 95% CI, 0.50 to 0.99; P = 0.045) (Figure 6). The median was not reached in either treatment arm. As the pre-specified alpha significance level for this interim analysis of OS was 0.0005, the result is not considered statistically significant at this time. However, a clear positive trend in the improvement in survival for patients treated with darolutamide can be concluded based on these results.

Note: The data cut-off for the final OS analysis has now been reached (15th November 2019). Analysis shows a statistically significant effect of darolutamide on overall survival duration, as per the hierarchical testing model. Results will be submitted to NICE as soon as fully available.

Figure 6: Kaplan-Meier estimates of overall survival in the ARAMIS study (interim analysis, data cut-off 3rd September 2018; FAS) (1)



No. at Risk													
Darolutamide	955	932	880	737	586	428	302	218	123	64	35	8	0
Placebo	554	529	467	394	307	214	154	110	56	34	14	2	0

The remaining secondary variables were pre-specified in the hierarchical testing scheme to be tested for significance if MFS and OS were both significant. As OS did not reach the pre-specified alpha significance level of 0.0005 for the primary efficacy analysis, the secondary efficacy variables time to pain progression, time to initiation of first cytotoxic chemotherapy and time to first SSE were not tested for significance (nominal p-values are provided for information only). However, as described above, a clear benefit in favour of darolutamide was observed in all other secondary endpoints.

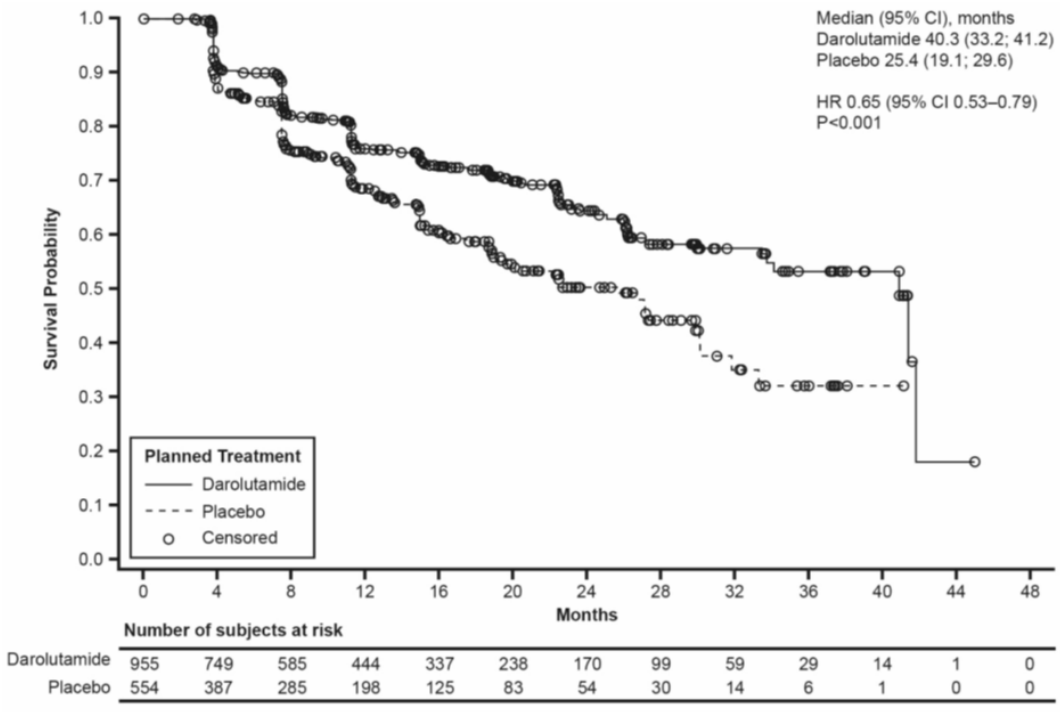
Note: Final OS analysis has now been performed, with an indication that significance has been reached for OS. This would have changed the significance of the other secondary endpoints in the hierarchical testing scheme (as listed above).

Time to pain progression

As of the cut-off date, 26.3% of the patients (251/955) in the darolutamide + ADT arm and 32.1% of the patients (178/554) in the placebo arm had pain progression. The median time to pain progression was 40.3 months (95% CI, 33.2 to 41.2]) in the darolutamide arm compared with 25.4 months (95% CI, 19.1 to 29.6) in the placebo

arm - a difference of 14.95 months in favour of darolutamide (HR of 0.65; 95% CI, 0.53 to 0.79; P<0.001).

Figure 7: Kaplan-Meier estimates of Time to Pain Progression in the ARAMIS study (data cut-off 3rd September 2018; FAS) (1)



Time to initiation of first cytotoxic chemotherapy

The results of the time to first cytotoxic chemotherapy analysis also favoured darolutamide (HR of 0.43 [95% CI, 0.31 to 0.60]; p<0.000001). Few events had occurred at the time of the primary completion analysis - 7.6% of patients in the darolutamide arm and 14.3% of patients in the placebo arm started treatment with cytotoxic chemotherapy for prostate cancer during the study. The median was not reached in the darolutamide + ADT arm. In the placebo arm the median time to initiation of first cytotoxic chemotherapy was 38.2 months (95% CI, 35.55 to 41.89).

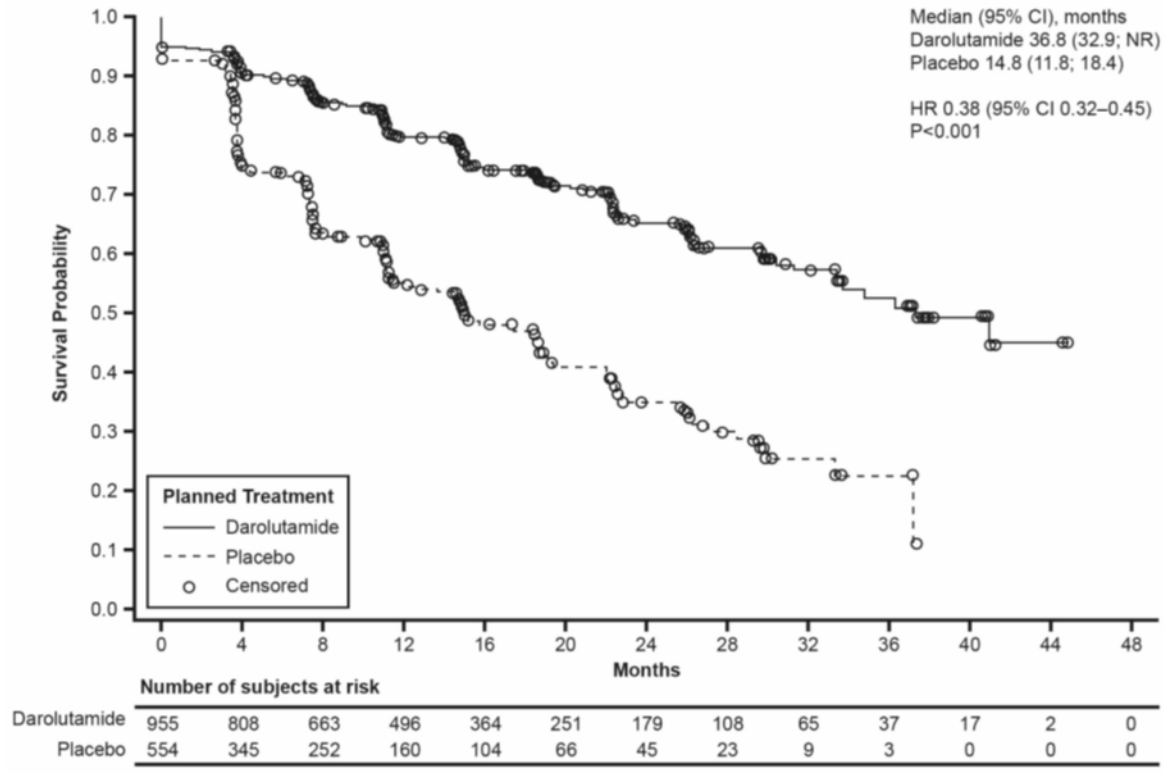
Figure 8: Kaplan-Meier estimates of Time to first cytotoxic chemotherapy in the ARAMIS study (data cut-off 3rd September 2018; FAS) (37)

Exploratory endpoints

Progression-free survival (PFS)

Median progression-free survival was 36.8 months in the darolutamide group and 14.8 months in the placebo group (HR=0.38; 95% CI, 0.32 to 0.45; P<0.001). Overall, [redacted] of the patients in the darolutamide arm and [redacted] of the patients in the placebo arm were reported with radiological disease progression or had died.

Figure 9: Kaplan-Meier estimates of Progression-free survival in the ARAMIS study (data cut-off 3rd September 2018; FAS) (1)



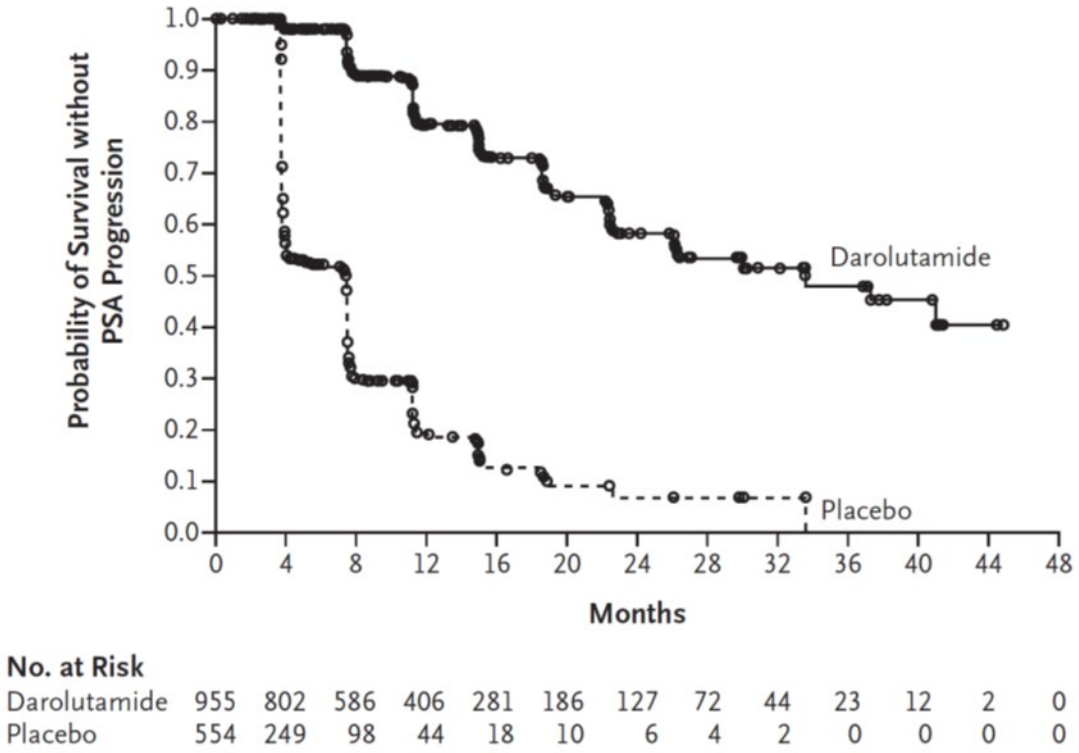
CI=confidence interval; HR=hazard ratio; NR=not reached;

Results of the PFS analysis with baseline metastasis censored were consistent with the analysis of PFS with baseline metastasis non-censored. Median PFS was [redacted] months ([redacted]) in the darolutamide + ADT arm and [redacted] months ([redacted]) in the placebo arm (HR = [redacted]).

Time to PSA progression

A smaller proportion of patients in the darolutamide arm ([redacted]) compared to the placebo arm ([redacted]) had PSA progression. The median time to PSA progression was 33.2 months with darolutamide and 7.3 months with placebo (HR=0.13; 95% CI, 0.11 to 0.16; P<0.001).

Figure 10: Kaplan-Meier estimates of Time to PSA progression in ARAMIS (data cut-off 3rd September 2018; FAS) (1)



FAS=full analysis set; PSA=prostate-specific antigen

Percent of patients with PSA response

The percent of patients with PSA response (decline of ≥50% from baseline) was higher in the darolutamide arm ([redacted], 95% CI, [redacted]) than in the placebo arm ([redacted], 95% CI, [redacted]), with a difference in response rates of [redacted] (95% CI, [redacted]).

Time to initiation of subsequent antineoplastic therapy (excluding cytotoxic chemotherapy)

The median time to initiation of subsequent antineoplastic therapy was not reached in either treatment arm, however, the analysis showed a positive trend in favour of darolutamide with 48 (5.0%) of patients in the darolutamide arm and 70 (12.6 %) of patients in the placebo arm having received subsequent anti-neoplastic therapy (excluding cytotoxic chemotherapy) (HR=0.33 (95% CI, 0.23 to 0.47; p<0.000001).

A post-hoc analysis of subsequent antineoplastic therapy and/or cytotoxic chemotherapy in patients who discontinued study treatment was performed. Overall, 35.5% [n=339] of the patients in the darolutamide arm and 63.9% [n=354] of the patients in the placebo arm had discontinued study treatment at the time of primary analysis data cut-off. Among patients who discontinued the trial regimen, 29.5% [i.e. 100/339] in the darolutamide group and 36.7% [i.e. 130/354] in the placebo group received subsequent approved therapy for metastatic castration-resistant prostate cancer (antineoplastic and / or cytotoxic therapy). All patients, and study personnel, including clinicians, remained blinded to treatment assignments during the double-blind part of the study (i.e. until data cut-off for primary analysis, 3rd September 2018), hence, subsequent therapies reported here were selected without knowledge of whether the patient had received darolutamide or placebo as study therapy. The most common subsequent treatments were docetaxel, abiraterone acetate, and enzalutamide (see Table 15).

Figure 11: Kaplan-Meier estimates of Time to initiation of subsequent antineoplastic therapy in the ARAMIS study (FAS) (39)

FAS=full analysis set

Table 15: First Subsequent Anticancer Therapy for Metastatic Castration-Resistant Prostate Cancer in Patients Who Discontinued Study Treatment (1, 39)

Patients, n (%)	**Darolutamide N=955**	**Placebo N=554**
Received study treatment	954 / 955 (99.9)	554 / 554 (100)
Discontinued study treatment	339/954 (35.5)	354 / 554 (63.9)
Received cytotoxic chemotherapy and / or antineoplastic therapy	100/339 (10.5)	130 /354 (23.5)
Preferred drug name: [b]		
Abiraterone, abiraterone acetate	13/100 (13.0)	23 (17.7)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Docetaxel	49 (49.0)	66 (50.8)
[redacted]	[redacted]	[redacted]
Enzalutamide	18 (18.0)	19 (14.6)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Patients, n (%)	Darolutamide N=955	Placebo N=554
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

ATC = Anatomical Therapeutic Chemical classification system; FAS = full analysis set; N = total number of patients (100%); n = number of patients with event; WHO-DD = World Health Organisation Drug Dictionary.

[redacted]

Many of the first subsequent antineoplastic / cytotoxic treatments listed in Table 15 would not be prescribed for metastatic CRPC in the UK. Also, radium-223 was not a listed post-progression therapy, but in the UK, it would be used in patients with bone metastases. The three most common subsequent antineoplastic / cytotoxic treatments in the study - docetaxel, abiraterone acetate, and enzalutamide – were suggested as the most likely prescribed first-line treatments post-progression on

ADT in the UK by an expert panel of oncologists (3). In addition, the panel stated that the majority of patients progressing on darolutamide (if it were available within the NHS) would be treated with docetaxel as first line in the metastatic setting in the UK. It is therefore reasonable to conclude that the first subsequent treatments in ARAMIS are consistent with what would have been prescribed in UK practice.

Health-related quality of life (HRQoL)

Maintenance of the health-related quality of life during ARAMIS was evaluated with FACT-P, EORTC-QLQ-PR25, EQ-5D-3L, and BPI-SF questionnaires.

In general, the results of the HRQoL endpoints, based on these questionnaires, demonstrated maintenance of HRQoL with a positive trend favouring darolutamide. Differences in least-squares mean time-adjusted AUC scores consistently favoured darolutamide and were significant for BPI-SF (pain severity and pain interference scores), FACT-P (Physical Well-Being, Emotional Well-Being, PCS, General, FACT-P total, and Trial Outcome Index), and the EORTC-QLQPR25 urinary symptoms subscale, although the clinically meaningful thresholds were not reached.

Table 16: Quality of Life outcomes (1)

LSM Time-Adjusted AUC (95% CI)	Darolutamide	Placebo	Difference	MID
BPI-SF Pain Interference [a]	1.1 (1.0, 1.3)	1.3 (1.2, 1.4)	-0.2 (-0.3, -0.1)	2
BPI-SF Pain Severity [a]	1.3 (1.1, 1.4)	1.4 (1.3, 1.6)	-0.2 (-0.3, -0.1)	2
FACT-P (total) [b]	112.9 (111.8, 114.0)	111.6 (110.5, 112.7)	1.3 (0.4, 2.1)	10
FACT-P PCS [b]	32.4 (31.9, 32.9)	31.8 (31.3, 32.2)	0.6 (0.3, 1.0)	3
EORTC-QLQ-PR25 [c] (urinary symptoms subscale)	23.7 (22.4, 25.0)	26.4 (25.1, 27.8)	-2.7 (-3.8, -1.7)	8
EQ-5D-3L Index Score [d]	0.8 (0.8, 0.8)	0.8 (0.8, 0.8)	0.01 (-0.00, 0.02)	-
EQ-5D-3L Visual Analogue Scale	73.3 (72.1, 74.4)	72.7 (71.5, 73.9)	0.6 (-0.3, 1.5)	-
AUC=area under the curve; BPI-SF=Brief Pain Inventory Short-Form; CI=confidence interval; EORTC-QLQPR25=European Organisation for Research and Treatment of Cancer Quality of Life;				

LSM Time-Adjusted AUC (95% CI)	Darolutamide	Placebo	Difference	MID
EQ-5D-3L=EuroQol 5-dimensions 3-levels; FACT-P=Functional Assessment of Cancer Therapy-Prostate; LSM=least-squares mean; MID=minimally important difference; PCS=prostate cancer subscale. Note: 95% CIs are not adjusted for multiplicity. [a] Higher scores represent more pain or interference, ranging from 0–10; a negative difference favours darolutamide. [b] Higher scores represent better health-related quality of life, ranging from 1–156; a positive difference favours darolutamide. [c] Higher scores reflect greater symptom impact, ranging from 0–100; a negative difference favours darolutamide. [d] Higher scores represent better health-related quality of life, ranging from −0.59 to 1; a positive difference favours darolutamide.				

EQ-5D-3L questionnaire – EQ-5D-3L index score

The percent of patients with deterioration of EQ-5D-3L index score at 16 weeks was similar in the darolutamide arm ([redacted]) compared to the placebo arm ([redacted]) with a difference in deterioration rate of [redacted] (95% CI, [redacted]).

The index score and VAS score results slightly favoured darolutamide but were not statistically significant and were not clinically meaningful, as they did not meet the MID thresholds. The results imply that quality of life was maintained on treatment.

Time to treatment discontinuation

This endpoint is used as an outcome in the model. Please refer to Section B.3.3 for further details.

The overall time under treatment at the time of the cut-off was longer in the darolutamide arm than in the placebo arm. The median treatment duration was 14.80 months for the 954 patients treated with darolutamide and 11.04 months for the 554 patients receiving placebo. The most frequent category of overall time under treatment was [redacted] months in both darolutamide ([redacted]) and placebo ([redacted]) arms. More than half of the patients in the darolutamide arm ([redacted] darolutamide vs. [redacted] placebo) received treatment >12 months to ≤30 months. The percentage of patients receiving treatment beyond 30 months was also [redacted] in the darolutamide arm ([redacted]) than in the placebo arm ([redacted]) (39).

B.2.7. Subgroup analysis

To determine whether demographic or baseline characteristics influenced the response to treatment, pre-planned subgroup analyses were performed for the primary endpoint MFS and for the secondary endpoint OS. Subgroup analyses were not performed for the sensitivity analyses. Subgroup analyses were based on the FAS analysis set. Descriptive statistics and hazard ratio with 95% CI were provided within each category, if there were sufficient patients in total within the subgroup across the treatment arms. All subgroups analyses were carried out using a non-stratified Cox model and log-rank test.

Subgroup analyses of interest:

Efficacy variables

- Baseline CRF PSADT (≤6 and >6 months)
- Baseline CRF osteoclast-targeted therapy (yes vs. no)
- Baseline PSA (ng/mL) (≤10; >10 to ≤20; >20) from the central laboratory
- Baseline PSA (ng/mL) (at or below median vs. above the median [median of all patients]) from the central laboratory
- Gleason score at diagnosis (<7 vs. ≥7)
- Age (years) (<65, 65 - 74, 75 - 84, ≥85)
- Geographical region (North America, Asia Pacific, ROW)
- Baseline presence of regional pathological lymph nodes (yes vs. no) by central imaging review
- Baseline ECOG performance status (0, 1)
- Race: White, Asian, Black or African American, Other; ethnicity 'Hispanic or Latino'
- Number of prior hormonal therapies (1, ≥2)

Adverse events were displayed by the following subgroups:

- Age (years): <65 vs. 65-74 vs. 75-84 vs. ≥85
- Geographical region: North America vs. Asia Pacific vs. ROW

- Renal function - eGFR at baseline:
  - normal (eGFR ≥90 mL/min) vs.
  - mildly impaired (60≤ eGFR <90 mL/min) vs.
  - moderately impaired (30≤ eGFR <60 mL/min), severely impaired (15≤ eGFR <30 mL/min) or end stage renal disease (eGFR <15 mL/min and not on dialysis, or requiring dialysis)
- Hepatic function at baseline:
  - normal (total bilirubin and AST ≤ ULN) vs.
  - mild impairment (total bilirubin > ULN to 1.5 x ULN or total bilirubin ≤ ULN and AST > ULN) vs.
  - moderate (total bilirubin > 1.5 to 3 x ULN, any AST) or severe impairment (total bilirubin > 3 x ULN, any AST)
- Concomitant statin use: no vs. yes, as determined by concomitant medication.

See Appendix E for a summary of results for subgroup analyses.

B.2.8. Meta-analysis

Not applicable. Evidence from only one RCT is relevant to the decision problem (i.e. ARAMIS study).

B.2.9. Indirect and mixed treatment comparisons

Indirect comparisons were not conducted for this appraisal. Standard treatment in routine clinical practice is androgen deprivation therapy (ADT). ADT was the comparator in the ARAMIS study, hence, in the model, direct comparisons can be made between darolutamide and standard treatment, using ARAMIS study results.

B.2.10. Adverse reactions

Based on the data from the Phase 3 randomised, double-blind ARAMIS study, darolutamide has a favourable safety profile in nmCRPC patients. The adverse drug reactions identified for darolutamide - fatigue, pain in extremity and rash - were generally mild and manageable. Treatment with darolutamide

does not increase the risk for specific safety concerns including fracture, falls, seizures, mental impairment and hypertension, which are known to be associated with currently existing therapeutic options for nmCRPC.

Overall, the data show that darolutamide is well tolerated with the incidence of TEAEs leading to permanent discontinuation of study treatment comparable in both darolutamide (8.9%) and placebo (8.7%) treatment arms.

Introduction to adverse event data

Evidence of the safety of darolutamide for the treatment of adult men with non-metastatic castration resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease is drawn from the ARAMIS study - an international multicentre phase III double-blind, randomised clinical trial (RCT).

Patients with nmCRPC are generally asymptomatic, therefore it is important that any treatment for nmCRPC must be well tolerated and not have a detrimental effect on patients' current health and quality of life.

The population for safety analysis In ARAMIS comprised all patients who received at least one dose of study medication. A total of 1508 patients, received either darolutamide or placebo concurrently with ADT (n=954 darolutamide 600mg b.i.d. and n=554 placebo). Baseline characteristics were similarly distributed to those of the population evaluable for efficacy.

Median time on treatment for patients in the safety analysis population was 14.8 months (darolutamide, [Min 0.00, Max 44.3]) and 11.0 months (placebo, [Min 0.1, Max 40.5]) (44), resulting in lower exposure in the placebo arm.

Note: To adjust for unequal lengths of study treatment duration between the two treatment arms in ARAMIS, event rates per 100 patient years were also summarised (total number of patients with events divided by the total treatment duration in years).

Summary of adverse events (AEs) (1, 44)

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) (v21.0) and were graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Overall, the incidence of treatment-emergent adverse events (TEAEs) was comparable between the darolutamide and placebo arms (83.2% vs. 76.9%, respectively). In most cases, TEAEs were of CTCAE grade 1 or 2 (as the worst grade), with a similar incidence between the darolutamide and placebo treatment arms (54.6% with darolutamide and 54.2% with placebo). Grade 3 or 4 TEAEs were reported in 24.7% and 19.5% of patients in the darolutamide and placebo treatment arms, respectively. Death (CTCAE grade 5) occurred in 3.9% (darolutamide) and 3.2% (placebo) patients, with one death in the darolutamide group and two deaths in the placebo group considered to be related to the trial regimen. Serious AEs (SAEs) were experienced by 24.8% of patients in the darolutamide arm and 20.0% in the placebo arm. Adverse events that led to a dose modification were higher in the darolutamide arm (14.2%) than in the placebo arm (9.4%). TEAEs that led to permanent discontinuation of study treatment occurred at a similar level in both darolutamide and placebo treatment arms (8.9% vs. 8.7%).

A summary of the TEAEs reported in ≥2% of patients in either treatment arm is presented in Table 17. Except for fatigue (12.1% vs. 8.7%), incidences of TEAEs were similar and below 10% in both treatment arms. The most frequent TEAEs reported at a higher incidence (≥1 percentage point difference) in the darolutamide arm compared to the placebo arm were fatigue (12.1% vs. 8.7%), diarrhoea (6.9% vs. 5.6%), hypertension (6.6% vs. 5.2%), pain in extremity (5.8% vs. 3.2%), anaemia (5.6% vs. 4.5%), hot flush (5.2% vs. 4.2%), peripheral oedema (4.1% vs. 3.1%), pollakiuria (4.0% vs. 2.9%), headache (3.9% vs. 2.5%), musculoskeletal pain (3.9% vs. 2.0%), dizziness (3.7% vs. 2.5%), weight decreased (3.6% vs. 2.2%), cough (3.0% vs. 2.0%), influenza (2.8% vs. 1.6%), upper respiratory tract infection (2.6% vs. 1.6%), and pyrexia (2.0% vs. 0.9%).

After adjustment, the incidences of most common TEAEs listed above were comparable between the treatment arms except for musculoskeletal pain, pyrexia

and pain in extremity which were higher in the darolutamide arm compared to the placebo arm. Considering that the majority of pyrexia events were reported in close association with bacterial infections and the absence of known association between androgen deprivation and febrile conditions, the observed imbalance in the incidence of pyrexia was not considered to have causal relationship to darolutamide treatment.

Pain in extremity and musculoskeletal pain were predominantly mild and manageable with no reports for serious events, permanent treatment discontinuations or dose reductions. Nevertheless, the higher incidence on darolutamide means that it has been added to Summary of Product Characteristics as an 'undesirable effect of darolutamide'.

In contrast, after exposure-adjustment, back pain, arthralgia, constipation, nausea, urinary tract infection, haematuria, falls, urinary retention, dysuria, urinary incontinence, upper abdominal pain, pelvic pain and hydronephrosis were reported less frequently in darolutamide-treated patients, compared with placebo treatment.

Table 17: Most common TEAEs and exposure-adjusted TEAEs occurring in ≥2% of patients in either arm of the ARAMIS study (SAF) (1, 44)

MedDRA PT Version 21.0	Darolutamide + ADT N=954		Placebo N=554	
	Total n (%)	EAIR per 100 PY[a]	Total n (%)	EAIR per 100 PY[a]
Any adverse event	794 (83.2)		426 (76.9)	
Fatigue	115 (12.1)	8.6	48 (8.7)	8.5
Back pain	84 (8.8)	6.3	50 (9.0)	8.8
Arthralgia	77 (8.1)	5.8	51 (9.2)	9.0
Diarrhoea	66 (6.9)	4.9	31 (5.6)	5.5
Hypertension	63 (6.6)	4.7	29 (5.2)	5.1
Constipation	60 (6.3)	4.5	34 (6.1)	6.0
Pain in extremity	55 (5.8)	4.1	18 (3.2)	3.2
Anaemia	53 (5.6)	4.0	25 (4.5)	4.4
Hot flush	50 (5.2)	3.7	23 (4.2)	4.1
Nausea	48 (5.0)	3.6	32 (5.8)	5.6
Urinary tract infection	47 (4.9)	3.5	28 (5.1)	4.9
Haematuria	41 (4.3)	3.1	27 (4.9)	4.8
Peripheral oedema	39 (4.1)	2.9	17 (3.1)	3.0

MedDRA PT Version 21.0	Darolutamide + ADT N=954		Placebo N=554	
	Total n (%)	EAIR per 100 PY[a]	Total n (%)	EAIR per 100 PY[a]
Pollakiuria	38 (4.0)	2.8	16 (2.9)	2.8
Headache	37 (3.9)	2.8	14 (2.5)	2.5
Musculoskeletal pain	37 (3.9)	2.8	11 (2.0)	1.9
Asthenia	36 (3.8)	2.7	19 (3.4)	3.3
Fall	36 (3.8)	2.7	23 (4.2)	4.1
Nasopharyngitis	36 (3.8)	2.7	21 (3.8)	3.7
Dizziness	35 (3.7)	2.6	14 (2.5)	2.5
Weight decreased	34 (3.6)	2.5	12 (2.2)	2.1
Urinary retention	33 (3.5)	2.5	36 (6.5)	6.3
Cough	29 (3.0)	2.2	11 (2.0)	1.9
Decreased appetite	28 (2.9)	2.1	16 (2.9)	2.8
Influenza	27 (2.8)	2.0	9 (1.6)	1.6
Insomnia	26 (2.7)	1.9	10 (1.8)	1.8
Upper respiratory tract infection	25 (2.6)	1.9	9 (1.6)	1.6
Abdominal pain	24 (2.5)	1.8	12 (2.2)	2.1
Dyspnoea	24 (2.5)	1.8	15 (2.7)	2.6
Atrial fibrillation	22 (2.3)	1.6	8 (1.4)	1.4
Blood creatinine increased	22 (2.3)	1.6	14 (2.5)	2.5
Dysuria	21 (2.2)	1.6	26 (4.7)	4.6
Gynaecomastia	19 (2.0)	1.4	6 (1.1)	1.1
Pneumonia	19 (2.0)	1.4	11 (2.0)	1.9
Pyrexia	19 (2.0)	1.4	5 (0.9)	0.9
Pruritus	16 (1.7)	1.2	11 (2.0)	1.9
Urinary incontinence	14 (1.5)	1.0	12 (2.2)	2.1
Abdominal pain upper	12 (1.3)	0.9	13 (2.3)	2.3
Pelvic pain	12 (1.3)	0.9	12 (2.2)	2.1
Hydronephrosis	10 (1.0)	0.7	13 (2.3)	2.3

CTCAE=common terminology criteria for adverse events; EAIR=exposure-adjusted incidence rate; MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients; n=number of patients with event; nmCRPC=non-metastatic castration-resistant prostate cancer; PT=Preferred term; SAF=safety analysis set; TEAE=treatment-emergent adverse event;

a EAIR of TEAEs, defined as the number of patients with a given TEAE divided by the total treatment duration of all patients in years. The rate is expressed in 100 patient years.

Note: a patient may have more than one entry.

Drug-related TEAEs

TEAEs considered study drug-related by the investigator occurred in 27.0% and 19.9% of patients in the darolutamide arm and placebo arm, respectively. Drug-related

events reported in ≥2% of patients in the darolutamide or placebo treatment arms, respectively, included fatigue (7.1% vs. 4.3%), hot flush (3.8% vs. 2.7%) and nausea (2.5% vs. 3.1%).

Treatment-emergent serious adverse events (TESAEs)

At least one SAE was reported for 24.8% of patients in the darolutamide arm and 20.0% of patients in the placebo arm. Most SAEs were reported in <1% of patients in both treatment arms. SAEs occurring in ≥1% of patients were urinary retention (1.6% vs. 3.2%, respectively; 1.1 vs. 3.2 patients per 100 years exposure), followed by pneumonia (1.4% vs. 1.1%; 1.0 vs. 1.1 exposure-adjusted) and haematuria (1.0% vs. 1.1%; 0.7 vs. 1.1 exposure-adjusted) (44).

An incidence rate of 13.8% and 11.0% Grade 3 SAEs was reported in darolutamide and placebo arms, respectively (deemed drug-related in 2.5% of patients in both treatment arms; hypertension [0.4% vs. 0.5%] and fatigue [0.2% vs. 0.2%]). Grade 4 SAEs were experienced by 2.0% of patients in the darolutamide arm and 1.6% of patients in the placebo arm; drug-related in 3 patients (0.3%) in the darolutamide arm (abnormal hepatic function, ischaemic stroke, and pulmonary embolism) and no patients in the placebo arm.

Adverse events of special interest

AEs known to occur with ADT or novel antiandrogens / second generation androgen-receptor inhibitors were analysed in detail as special topics (see Table 18). Darolutamide was not associated with a higher incidence of seizures, falls, fractures, mental impairment / cognitive disorders, depressed mood disorders or hypertension than placebo. Also, no evidence was found for an increased risk of cerebrovascular disorders when darolutamide treatment is added to ADT. On analysis, the observed slight difference between the treatment arms for flushing / hot flushes, and gynaecomastia were not considered clinically meaningful, and indeed, the EAIR for these events was very similar between treatment arms.

Rash is a known adverse drug reaction associated with existing anti-androgen therapy and evidence suggests causal role of darolutamide in the occurrence of

rash. Darolutamide treatment in combination with ADT contributed to a higher prevalence rate of fatigue/asthenic conditions.

Medical history of cardiac disorders represented the main driver of the TEAE reporting within the groupings ‘coronary artery disorders’ and ‘heart failures’. Darolutamide was not found to increase the risk of cardiovascular disorders when added to ADT.

Table 18: Incidence of TEAEs and exposure-adjusted TEAEs for special topics in ARAMIS study (SAF) (1, 39, 44)

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

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]	

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.
- 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'

Laboratory values and Vital signs (36)

Generally, these values were similar between darolutamide + ADT and placebo treatment arms except for:

- neutrophil count decreased (darolutamide + ADT 19.6% vs. placebo 9.4%),

- white blood cell (WBC) decreased (darolutamide + ADT 19.7% vs. placebo 11.8%),
- AST increased (darolutamide + ADT 22.5% vs. placebo arm 13.6%).

The occurrence of neutropenia and decrease WBC did not result in an increase in febrile neutropenia (darolutamide + ADT = 0 cases; placebo = 1 grade 3 case).

Darolutamide treatment also seems to contribute to mild and reversible hyperbilirubinemia, characterised by an increase of indirect bilirubin with values reverting to normal once treatment is stopped. There is no evidence that treatment with darolutamide triggers drug-induced liver injury.

Adverse events leading to premature permanent discontinuation of study drug

A similar proportion of patients discontinued study treatment due to AEs in the darolutamide + ADT group (8.9%) and the placebo group (8.7%). The most common events leading to treatment discontinuation were cardiac failure (0.4% vs. 0.7%) and death (0.4% vs. 0.2%). Dose modifications (interruption, delay or reduction) were required for 15.2% of patients in the darolutamide + ADT arm and for 9.7% in the placebo arm, mainly due to AEs. The most common TEAEs leading to dose interruption in the darolutamide +ADT arm were hypertension (darolutamide + ADT 0.6% vs. placebo 0%), diarrhoea (0.5% vs. 0.2%) and pneumonia (0.5% vs. 0.4%), and for the placebo arm were urinary retention, nausea, and fatigue. The most commonly reported TEAEs leading to dose reduction in both darolutamide + ADT and placebo arms were fatigue, hypertension, and nausea. **Deaths**

TEAEs resulting in death occurred in 3.9% and 3.2% of patients in the darolutamide + ADT and placebo arms, respectively. In 0.1% (1 patient with small intestinal perforation) and 0.4% (1 patient with myocardial infarction and intracranial haemorrhage each) of darolutamide + ADT and placebo patients, respectively, these events were considered drug-related by the investigator. Overall, deaths (due to any reason, at any time of the study) were reported in 8.3% and 10.5% of patients,

respectively. Prostate cancer was reported as a reason for death in 38.0% of all deaths in the darolutamide + ADT arm and in 43.1% of all deaths in the placebo arm.

Table 19: Treatment-emergent grade 5 Adverse events by MedDRA Preferred Term (SAF) (1)

Grade 5 adverse events patients, n (%)	Darolutamide + ADT N=954	Placebo N=554
Any	37 (3.9)	18 (3.2)
Acute myocardial infarction	1 (0.1)	0
Angina pectoris	1 (0.1)	0
Cardiac arrest	2 (0.2)	3 (0.5)
Cardiac disorder	1 (0.1)	0
Cardiac failure	3 (0.3)	3 (0.5)
Acute cardiac failure	1 (0.1)	0
Coronary artery disease	1 (0.1)	0
Hypertensive heart disease	0	1 (0.2)
Myocardial infarction	0	1 (o.2) [a]
Diarrhoea	1 (0.1)	0
Perforation of the small intestine	1 (0.1) [a]	0
Death	4 (0.4)	1 (0.2)
General physical health deterioration	2 (0.2)	0
Sudden cardiac death	1 (0.1)	0
Sudden death	1 (0.1)	0

Subgroup analyses

Subgroup analyses for TEAEs were performed for age, race, geographical region, renal function at baseline (mild, moderate or severe renal impairment), hepatic function at baseline (mild to moderate hepatic impairment) and concomitant statin use. There was no clinically relevant effect on patient safety of darolutamide + ADT exposure in the investigated subgroups or between the darolutamide + ADT and placebo arms.

Supportive analyses

[redacted]

[redacted] (36).

[redacted]

Long-term treatment

In ARAMIS, the darolutamide treated nmCRPC patients had a median overall time under treatment of 14.8 months, the longest time being 44.3 months. More than half of the patients, 51.7% in the darolutamide arm and 36.8% in the placebo arm, received treatment >12 to ≤30 months. No evidence was found for increased risk of effects with delayed onset or with cumulative character when darolutamide treatment was added to ADT (36).

Overview of the safety of the technology in relation to the decision problem

The population defined in the decision problem exactly matches the study population of the phase III trial ARAMIS i.e. non-metastatic castration-resistant prostate cancer. Therefore, it is anticipated the safety profile of darolutamide described within this submission will be similar to that in routine clinical practice in the UK.

The majority of patients receiving darolutamide in the ARAMIS study tolerated the full dose of study drug without the need for discontinuation, delay, interruption, or reduction of study drug. The incidence and pattern of TEAEs was similar in both treatment arms (i.e. darolutamide and placebo), indicating that when darolutamide is added to standard androgen deprivation therapy, it does not cause any increased risk. This is important given that patients with nmCRPC are generally asymptomatic and additional therapy at this stage should aim to conserve patients' current health and quality of life, to no detrimental effect.

B.2.11. Noted 'undesirable effects' of darolutamide therapy were fatigue, pain in extremity, and rash, which were generally mild and manageable. Laboratory abnormalities of decreased neutrophil count, increased AST and increased bilirubin were either transient or reversible after treatment discontinuation and were not associated with any clinically relevant signs or symptoms. Ongoing studies

A total of 815 patients continued study treatment after the primary completion date of the ARAMIS study (Darolutamide arm: n=615; placebo arm n=200). An open-label part of the study, offering patients in the placebo arm the opportunity to benefit from darolutamide treatment, started officially on 30 OCT 2018. A follow-up clinical study report will be prepared when the study has been completed.

B.2.12. Innovation

Currently there are two second-generation androgen receptor inhibitors (ARIs) (enzalutamide, apalutamide) approved in Europe for the treatment of high-risk nmCRPC, neither of which are recommended by NICE for nmCRPC. In absence of any other treatment options at this stage of the prostate cancer management pathway, patients continue to take ADT as the standard therapy.

As the first specific first-line therapy for nmCRPC to be recommended by NICE, the introduction of darolutamide treatment for high-risk nmCRPC patients to delay development of metastases / symptoms of disease progression would bring about a

step-change in the management of nmCRPC. Darolutamide is considered innovative compared with other ARIs for several reasons:

1. **Favourable safety profile** - Darolutamide is structurally distinct compared to the other ARIs, consisting of two diastereomers, with a high binding affinity and selectivity to the androgen receptor. Its distinct structure and higher polarity, offers the potential for fewer and less severe toxic central nervous system (CNS)–related effects than apalutamide and enzalutamide, because of its **low penetration of the blood brain barrier** and low binding affinity for γ-aminobutyric acid type A ($GABA_A$) receptors, as shown in preclinical studies (4, 35) and confirmed in the ARAMIS trial.

   In the ARAMIS study, there was no incremental risk with the addition of darolutamide to ADT for AEs such as fracture, fall, seizure, hypertension, weight decrease, mental impairment, diabetes and hyperglycaemia, cardiovascular disorders, cerebrovascular disorders, vasodilatation and flushing, depressed mood disorders, and breast disorders/gynaecomastia, which are associated with the currently existing therapeutic options for patients with nmCRPC. Clinical trials evaluating the efficacy and safety of enzalutamide and apalutamide in the nmCRPC population excluded subjects with a history of seizure or any condition that might predispose a patient to a seizure, however CNS toxicity was observed in clinical trials for these therapies, manifesting as seizures, falls, fractures, and, more commonly, fatigue (31, 32). Indeed, an independent network meta-analysis of safety results from the pivotal RCTs for darolutamide, enzalutamide and apalutamide revealed significant heterogeneity in effect among ARis (45). In particular, darolutamide was associated with a lower risk for falls (vs. enzalutamide: OR 0.29, 95% CI 0.14-0-60; vs. apalutamide: OR 0.48, 95% CI 0.25-0.91); fatigue all grades (vs enzalutamide: OR 0.59, 95% CI 0.39-0.88) and severe (vs. enzalutamide: OR 0.10, 95% CI 0.02-0.60); hypertension (vs. enzalutamide: OR 0.51, 95% CI 0.27-0.98); mental impairment (vs. enzalutamide: OR 0.15, 95% CI 0.04-0.58; vs. apalutamide: OR 0.24, 95% CI 0.06-0.90).

2. **Results from Physician, Patient and Caregiver Preference studies indicate that treatments such as darolutamide, with lower AE burdens, in particular, a reduction of fractures, falls and cognitive problems are preferred for largely asymptomatic nmCRPC patients and that, in order to avoid AEs and optimise quality of survival, patients, physicians and caregivers are willing to trade substantial amounts of OS (46, 47).** Discrete choice experiment methods were used to explore how US Oncologists, Urologists, patients and caregivers perceive the benefit (i.e. overall survival, time to pain progression) versus risks (i.e. adverse events, in particular, fatigue, skin rash, cognitive problems, falls and fractures) of nmCRPC treatments.

   The online survey included 14 treatment choice questions, each comparing 2 hypothetical medication profiles, which varied in terms of 5 safety (frequency or severity of adverse events [AEs]: fatigue, skin rash, cognitive problems, serious falls, and serious fractures) and 2 efficacy (duration of overall survival [OS] and time to pain progression) attributes. These attributes were selected via qualitative interviews and pre-testing with physicians, patients, and caregivers. A main-effects random parameters logit model was used to estimate preference weights and importance scores for each attribute.

   - **Physicians** - 74 oncologists and 75 urologists completed the survey. Among safety attributes, physicians were most concerned with cognitive problems, fractures, and fatigue. Physicians placed 36% more importance on reducing cognitive problems from severe to none compared to improving OS by 12 months instead of 3 months. On average, physicians were willing to trade off 7.1 months of OS for a reduction in fatigue severity from severe to mild/moderate and 0.8 months of OS for a reduction in fatigue from mild/moderate to none. Physicians were willing to trade off approximately 5.0 and 4.2 months of OS for reductions in fracture risk from 8% to 5%, and 5% to 0%, respectively.

- **Patients and Caregivers** - 143 nmCRPC patients and 149 caregivers were included in the analysis. All viewed safety attributes in the following decreasing order of importance: fractures, falls, cognitive problems, fatigue, and rash. Compared to a reduction in rash severity from moderate to none, a similar reduction in cognitive problems severity was considered nearly as important by patients but twice as important by caregivers. On average, patients were willing to trade 5.8 and 4.0 months of OS to reduce the risks of serious fractures and falls, respectively, from 3% to 0%; the corresponding figures caregivers were willing to trade were 6.6 and 5.4 months of OS. Of note, 8.4% of pts and 14.8% of caregivers consistently chose the treatment profile with the lowest fall or fracture risk, regardless of the other attributes' values.

Physicians making treatment decisions for largely asymptomatic nmCRPC patients were willing to trade substantial amounts of survival to avoid AEs. This was also the case from a patient or caregiver's perspective, where treatments with lower AE burdens were also preferred in particular, a reduction of fractures, falls and cognitive problems.

Darolutamide provides the opportunity to optimise the overall quality of the patients' survival. This is due to the difference in safety profiles between existing approved treatments for nmCRPC and darolutamide in the attributes of most importance to patients and caregivers (i.e. fractures, falls and cognitive problems). However, as physician, patient and caregiver preferences in relation to the safety profile are not captured in the QALY calculation within this submission, it seems the benefits of darolutamide may not be fully captured.

3. **Flexible drug-drug interaction (DDI) profile (see Appendix C - Nubeqa® (darolutamide) Draft Summary of Product Characteristics) (36, 44) -** Darolutamide has no clinically meaningful effect on P-gp substrates or those metabolised via CYP3A4 or any other CYP enzyme. As most medications are substrates of CYP enzymes or have an inhibitory effect on these enzymes or on a transporter like P-gp, darolutamide will allow flexibility for concomitant

use with medications typically used in the nmCRPC population. This will positively impact clinical practice by improving the management of prostate cancer treatment in an elderly population with co-morbidities where polypharmacy is the norm. This contrasts with enzalutamide and apalutamide, where the Summaries of Product Characteristics (SmPCs) [accessed January 2020] carry more extensive lists of medicines to be avoided or used with care due to expected interactions with many commonly used medications that are sensitive substrates of enzymes or transporters, which may lead to loss of efficacy of these medications.

Co-administration of darolutamide with CYP3A4, P-gp and BCRP inhibitors does not result in a clinically relevant increase of darolutamide plasma concentrations, hence, darolutamide can be used concomitantly with CYP3A4, BCRP and P-gp inhibitors without the need for dose adjustments.

Darolutamide has no clinically meaningful effect on substrates that are metabolised via CYP3A4 or any other CYP enzyme (e.g. warfarin, L-thyroxine, omeprazole).

Darolutamide is an inhibitor of Breast Cancer Resistance Protein (BCRP) and Organic Anion Transporting Polypeptides (OATP) 1B1 and 1B3 and can be used concomitantly with medications that are substrates of OATP1B1, OATP1B3 or OAT3, and BCRP (e.g. methotrexate, sulfasalazine, fluvastatin, atorvastatin, pitavastatin).; however patients should be monitored for adverse reactions as co-administration with darolutamide may increase the plasma concentration of these substrates. In addition, the related recommendation in the product information of these substrates should be followed when co-administered with darolutamide.

Darolutamide may also be given concomitantly with P-gp substrates (e.g. dabigatran etexilate, digoxin, verapamil or nifedipine) without a clinically relevant drug-drug interaction.

Note: Use of strong CYP3A4 and P-gp inducers during treatment with darolutamide may decrease the plasma concentration of darolutamide and is not recommended, unless there is no therapeutic alternative. Co-administration with rosuvastatin should be avoided unless there is no therapeutic alternative. Use of strong CYP3A4

inducers and P-gp inducers (e.g. carbamazepine, phenobarbital, St. John's Wort, phenytoin, and rifampicin) during treatment with darolutamide is also not recommended, unless there is no therapeutic alternative. Selection of an alternate concomitant medicinal product, with no or weak potential to induce CYP3A4 or P-gp should be considered.

B.2.13. Interpretation of clinical effectiveness and safety evidence

Principal findings from the clinical evidence: clinical benefits and harms

The main evidence for the clinical effectiveness of darolutamide in the treatment of patients with nmCRPC who are at high risk for developing metastases, is provided by the phase III, international, randomised, double-blind, placebo-controlled study, ARAMIS. Patients with nmCRPC are typically asymptomatic and the key therapeutic goal in nmCRPC is delaying the onset of metastases without detriment to patients' quality of life. This goal is important to both patients and UK clinicians (3).

Aligned with the therapeutic aims in the management of nmCRPC, the primary endpoint of ARAMIS was metastasis-free survival (MFS). Darolutamide was found to provide a superior and statistically significant improvement in MFS when compared with placebo, with a median MFS of 40.4 months in the darolutamide arm compared with 18.4 months in the placebo arm (HR=0.41; 95% CI, 0.34 to 0.50; p<0.001), signifying a 59% reduction in the risk of metastasis or death. The magnitude of the MFS benefit was maintained across all subgroup analyses, suggesting broad applicability of the treatment in routine clinical practice.

The clinical benefit of darolutamide was further supported with analysis of the secondary endpoint, overall survival (OS). At the time of the data cut-off for the primary efficacy analysis, only 136 out of the 240 OS events planned for the final OS analysis had occurred. Both study arms exhibited a low number of events: 78 (8.2%) in the darolutamide arm and 58 (10.5%) in the placebo arm, with the median OS not reached in either treatment arm (HR=0.71; 95% CI, 0.50 to 0.99; p=0.045). Subgroup analyses of OS (at the time of primary efficacy analysis) were consistent with and supportive of the clear positive trend for darolutamide compared to placebo seen in the main analysis of OS. *Note: The data cut-off for the final OS analysis has*

now been reached (15th November 2019). Analysis shows a statistically significant effect of darolutamide on overall survival duration, as per the hierarchical testing model. Results will be submitted to NICE as soon as fully available (48).

Results of analyses of remaining secondary endpoints time to pain progression (Median time: 40.3 months darolutamide vs. 25.4 months placebo; HR=0.65; 95% CI, 0.53 to 0.79), time to initiation of first cytotoxic chemotherapy (HR=0.43; 95% CI, 0.31 to 0.60), and time to first SSE (HR=0.43; 95% CI,0.22, 0.84]) as well as all additional endpoints supported the benefit of darolutamide over placebo that was observed for the MFS primary endpoint. Additional endpoints included PFS (median PFS times of 36.8 months and 14.8 months; HR= 0.38; 95% CI, 0.33 to 0.45; p<0.001), time to initiation of subsequent antineoplastic therapy, time to PSA progression (median times of 33.2 months and 7.3 months; HR= 0.13; 95% CI, 0.11 to 0.16; p<0.001), and PSA response rate.

The positive clinical effects of darolutamide were achieved with maintenance of patient health-related quality of life (HRQoL), as measured by BPI-SF, FACT-P, EORTC-QLQ-PR25, and EQ-5D-3L questionnaires, and a favourable safety profile. The adverse drug reactions identified for darolutamide - fatigue, pain in extremity and rash - were generally mild and manageable. Overall, darolutamide treatment was well tolerated, with no meaningful differences compared to the placebo arm (including falls, fractures, seizures, cognitive disorders, and hypertension which are associated with currently existing therapeutic options for nmCRPC), and adverse events (AEs) representative of the underlying disease and age of the patient population. This is contrast to other second generation ARIs. An independent network meta-analysis of safety outcomes from the pivotal RCTs for darolutamide, enzalutamide and apalutamide revealed significant heterogeneity in effect among ARIs (45). In particular, darolutamide was associated with a lower risk for falls (vs. enzalutamide: OR 0.29, 95% CI 0.14-0-60; vs. apalutamide: OR 0.48, 95% CI 0.25-0.91); fatigue all grades (vs enzalutamide: OR 0.59, 95% CI 0.39-0.88) and severe (vs. enzalutamide: OR 0.10, 95% CI 0.02-0.60); hypertension (vs. enzalutamide: OR 0.51, 95% CI 0.27-0.98); mental impairment (vs. enzalutamide: OR 0.15, 95% CI 0.04-0.58; vs. apalutamide: OR 0.24, 95% CI 0.06-0.90).

The significant MFS benefit observed in the primary analysis of the ARAMIS study and data from supportive efficacy analyses combined with the favourable safety profile support a positive benefit-risk profile for darolutamide in the treatment of patients with high-risk nmCRPC.

Strengths and limitations of the clinical evidence base

A key strength of the clinical evidence is that the ARAMIS study was a well-designed trial, with sufficient patient numbers to enable a robust statistical analysis as well as detection of safety signals. The selection of endpoints in the study accurately reflects the main risks and issues experienced by patients with nmCRPC in respect of the occurrence and problematic symptoms of metastases and progressing prostate cancer (e.g. metastatic-free survival, overall survival, time to PSA progression, times to pain progression / opioid use / cytotoxic therapy, progression-free survival, HRQoL). This has been corroborated by expert UK treating clinicians(3). Endpoint assessment was performed via standard, validated measures - which included questionnaires for HRQoL - and the main efficacy analyses were based on independent blinded central imaging review.

The study demonstrated the efficacy and safety of darolutamide 600mg bid added into ADT in the high-risk nmCRPC patient population, with efficacy and safety in the overall patient group corroborated by all subgroup and sensitivity analyses. Additionally, ARAMIS efficacy results are consistent with findings from previous trials of other second-generation ARIs. Median MFS in ARAMIS was 40.4 months in the darolutamide arm compared with 18.4 months in the placebo arm (HR=0.41; 95% CI, 0.34 to 0.50; p<0.001). In the PROSPER study comparing enzalutamide with placebo, the median MFS was 36.6 months in the enzalutamide group versus 14.7 months in the placebo group (HR=0.29; 95% CI, 0.24 to 0.35; P<0.001) (32). Apalutamide was investigated in the SPARTAN study, with a median MFS of 40.5 months as compared with 16.2 months achieved in the placebo group (HR=0.28; 95% CI, 0.23 to 0.35; P<0.001) (31). A further strength of the evidence on darolutamide in comparison with other ARIs is that darolutamide was not associated with a higher incidence of seizures, falls, fractures, mental impairment / cognitive disorders, depressed mood disorders or hypertension than placebo in the ARAMIS

study, whereas these AEs are associated with the currently existing therapeutic options for nmCRPC (31, 32, 45). This may, in part, be linked to its distinct structure and low penetration of the blood brain barrier (4, 35). A consequence of this means that the ARAMIS study was able to include patients with previous seizure or conditions predisposing to seizure, unlike the trials for enzalutamide and apalutamide (31, 32) which excluded patients with a history of seizure or any condition that might predispose to a seizure. Physician, patient and caregiver preference studies on treatments of nmCRPC demonstrate the importance of treatments with lower AE burdens by a willingness to trade substantial amounts of survival to avoid AEs, and in particular, a reduction of fractures, falls and cognitive problems (46, 47).

With regard to the ARAMIS trial population, consistent efficacy was observed across all nmCRPC patients regardless of geography. However, as Black African-American males are known to carry a higher risk of developing prostate cancer (3), a limitation of the ARAMIS trial may be the underrepresentation of Black African-American patients (n=52). It was suggested, however, by a group of expert UK clinicians that it is well documented that Black African-American patients often present later in the disease setting (i.e. they have already developed metastases), which might explain the smaller numbers seen in the ARAMIS study (3).

ADT was selected as the most relevant comparator in the ARAMIS study, being the most established and consistent comparator arm in trials for this indication and also the treatment of choice in guidelines at the time of trial design. Newer recently approved treatments for patients with nmCRPC at high-risk of metastases i.e. enzalutamide and apalutamide, are becoming standard of care in international guidelines in combination with ADT, however, these are not integrated into standard UK clinical practice for treatment of nmCRPC, and therefore do not represent suitable comparators in this submission.

The analysis of overall survival is an interim analysis, due to an insufficient number of events being reached for the endpoint at the time of the primary efficacy analysis for the ARAMIS study. After 136 deaths out of the planned 240 (78 in the darolutamide group and 58 in the placebo group), darolutamide was associated with

a lower risk of death than placebo. However, data cut-off for the final OS analysis has now been reached (15th November 2019) and there is a significant difference in OS favouring patients receiving darolutamide. These results will be supplied to NICE as soon as they are available.

Relevance of the evidence base to the decision problem

Population in the decision problem: Adults with non-metastatic hormone-relapsed prostate cancer (nmHRPC).

The population considered in the evidence base within this submission is 'adults with nmCRPC who are at high risk of developing metastatic disease' which is the anticipated licence indication for darolutamide. In January 2013, NICE and the Department of Health agreed that the term 'castration resistant prostate cancer' would be replaced with 'hormone relapsed prostate cancer' (HRPC) in all its appraisals from January 2013 onwards. For purposes of this submission, HRPC and CRPC are interchangeable.

Evidence within the submission relates to patients with high-risk nmCRPC. All patients with nmCRPC are at risk of metastasis, but those considered to be at highest risk, and therefore those in most need of additional treatment, are those with a shorter PSA doubling time (PSADT) (i.e. ≤10 months) and increasing PSA levels and/or PSA velocity (see section 1.3). An expert panel of Oncologists confirmed that this definition of a high-risk patient population matches that in UK clinical practice.(3) In line with prostate cancer guidelines, other patients with nmCRPC are typically managed with continued ADT and active surveillance (18, 26, 27).

ARAMIS trial patients were drawn mainly from North America ([redacted] from the US), the Asia Pacific ([redacted]%) and Europe ([redacted]%), including [redacted] clinical trial centres in the UK, which randomised a total of [redacted] patients. Subgroup analyses of efficacy and safety parameters demonstrated consistent effect across all nmCRPC patients regardless of geography. Mean age of patients in ARAMIS was 74 years, similar to the mean age of CRPC patients identified in a study using a UK primary care database. Given the large cohort of patients being drawn from the US and Europe in the ARAMIS study, it is likely the ARAMIS study population will be generalisable to

the population found in clinical practice in England. This was agreed by a group of expert UK oncologists (3).

Comparator: Androgen deprivation therapy (ADT).

This is the most internationally recognised drug treatment for non-metastatic prostate cancer, including nmCRPC, and hence the most relevant comparator for a trial investigating new therapies in nmCRPC.

Intervention: Darolutamide + ADT

Darolutamide is not yet licensed for use in the UK in high-risk nmCRPC, however, when it becomes available it will be prescribed and used in the same way as in the ARAMIS study:

- i.e. 600 mg darolutamide (two tablets of 300 mg) taken twice daily, equivalent to a total daily dose of 1200 mg with medical castration with a luteinising hormone-releasing hormone (LHRH) analogue continued during treatment of patients not surgically castrated (see Appendix C. draft SMPC).

Thus, patients in clinical practice in England, receiving the licenced dose of darolutamide, would therefore be expected to respond to treatment in a similar way to those studied in ARAMIS.

Relevance of the outcomes assessed in clinical trials to clinical benefits experienced by patients in routine clinical practice

Endpoints assessed in the ARAMIS study included metastasis-free survival (MFS), overall survival (OS), time to pain progression, time to initiation of first cytotoxic chemotherapy, progression-free survival, time to PSA progression and PSA response, and health-related quality of life (HRQoL), all commonly used efficacy endpoints in non-metastatic and metastatic prostate cancer clinical trials. Results for these endpoints are presented in section B 2.6 and summarised above (section B 2.13.1).

The gold standard endpoint for many oncology trials is overall survival, however in prostate cancer it is now formally recognised that evolution from nmCRPC to

metastatic disease is a clinically relevant event. On this basis, the FDA Oncologic Drugs Advisory Committee (ODAC) discussed endpoints in therapies for nmCRPC in 2011 and introduced metastasis-free survival as a new and suitable surrogate endpoint for OS, especially in nmCRPC trials (41). Although the FDA recommended that MFS could be used as an endpoint in clinical trials, the clinical benefit of a drug would require a substantial magnitude of improvement and a favourable benefit–risk evaluation, given the typically asymptomatic status of patients with nmCRPC. Darolutamide treatment provided a statistically significant improvement in MFS compared to placebo with a median MFS was 40.4 months in the darolutamide arm compared with 18.4 months in the placebo arm (HR=0.41; 95% CI, 0.34 to 0.50) and the inclusion of HRQoL endpoints and safety analyses in ARAMIS confirmed a favourable benefit-risk evaluation.

In prostate cancer, development of metastases is often associated with pain, rises in PSA, a diminished quality of life, more frequent use of additional cytotoxic or antineoplastic therapies and death. Outcomes in ARAMIS therefore focus on these aspects of disease progression to measure the effect of darolutamide in delaying them – these are directly relevant to patients within clinical practice.

In summary, the clinical evidence related to darolutamide demonstrates it to be a highly effective treatment option for nmCRPC patients, with strong MFS benefit, supported by a favourable safety profile.

B.3. Cost effectiveness

B.3.1. Published cost-effectiveness studies

Full details of the systematic review for published cost-effectiveness studies in adults with nmHRPC/nmCRPC are reported in Appendix G. In summary, of the identified studies only five met the inclusion criteria and were included in this review, although none of these investigated the cost-effectiveness of darolutamide.

Of the five publications, four were health technology assessment (HTA) submissions: the Canadian Agency for Drugs and Technologies in Health appraisals for apalutamide (49) and enzalutamide in nmCRPC (50), the NICE appraisal for enzalutamide in nmCRPC (2) and the US Institute for Clinical and Economic Review report on antiandrogen therapies (referred to as androgen deprivation therapy [ADT]) for nmCPRC (51). One published abstract, for the International Society for Pharmacoeconomics and Outcomes Research, related to the cost-effectiveness of apalutamide for nmCRPC in the US was also identified (52). All studies considered metastases and/or progression in their definition of model health states.

A summary of the identified cost-effectiveness studies is provided in Table 20.

Table 20: Summary list of published cost-effectiveness studies

Study name	Treatment	Country	Type of study Type of model	Cost year Currency Discount rate	Health economic perspective Time horizon Cycle length	Model health states and definition
CADTH Enzalutamide (53)	• Enzalutamide + ADT • Apalutamide + ADT vs bicalutamide + ADT vs placebo (ADT alone)	Canada	• CUA • Markov model	• 2018 • Canadian dollar (C$) • NR	• Healthcare payer perspective • 10 years • 1 month	The model was based on three health states: • nmCRPC • Progressed mCRPC (mCRPC was further split into first-line PD1, second-line PD2, and third-line PD3) • Death
NICE Enzalutamide (2)	• Enzalutamide + ADT • ADT	UK	• CUA • Semi-Markov model combined with partitioned-survival modelling	• NR • Pound sterling (£) • 3.5%	• NHS and Personal Social Services perspective • Lifetime (20 years) • 1 month	The following health states were considered: • nmHRPC • mHRPC • Death Three Markov sub-health states are incorporated within the mHRPC health state: pre-chemo (PD1), during chemo (PD2) and post-chemo (PD3) representing first-,

Study name	Treatment	Country	Type of study Type of model	Cost year Currency Discount rate	Health economic perspective Time horizon Cycle length	Model health states and definition
						second-, and third-line treatment options for mHRPC, respectively
CADTH Apalutamide (54)	• Apalutamide + ADT • ADT monotherapy	Canada	• CUA • Partitioned-survival model	• 2018 • Canadian dollar (C$) • NR	• Government perspective • 15 years • NR	The model was based on three health states: • MFS • mCRPC • Death
ICER Anti-androgens (51)	• Apalutamide • Enzalutamide • Continued ADT without antiandrogen therapy	US	• CUA • A hybrid partitioned-survival and Markov model	• 2018 • US dollar (US$) • 3%	• US health sector perspective and societal perspective • Lifetime • 1 month	Four health states were used: • MFS • Asymptomatic progression • Symptomatic progression • Death
Zhou et al., 2018 (52)	• Apalutamide • Placebo	US	• CUA • Markov model	• NR • US dollar (US$) • NR	• US societal perspective • NR • 1 month	The model was based on three health states: • Stable disease • Progressed disease • Death

Key: ADT, androgen deprivation therapy; CADTH, Canadian Agency for Drugs and Technologies in Health; CUA, cost–utility analysis; ICER, Institute for Clinical and Economic Review; mCRPC, metastatic castration-resistant prostate cancer; MFS, metastasis-free survival; mHRPC, metastatic hormone-resistant prostate cancer; NHS;

Study name	Treatment	Country	Type of study Type of model	Cost year Currency Discount rate	Health economic perspective Time horizon Cycle length	Model health states and definition
National Health Service; NICE, National Institute for Health and Care Excellence; nmCRPC, non-metastatic castration-resistant prostate cancer; nmHRPC, non-metastatic hormone-resistant prostate cancer; NR, not reported; PD, progressive disease; vs, versus.						

B.3.2. Economic analysis

Patient population

In line with the anticipated European Medicines Agency marketing authorization, the patient population for the economic analysis is adult men with nmCRPC who are at high risk of developing metastatic disease (55). This corresponds to the patient population enrolled in the trial; that is men with nmCRPC and are at high-risk of developing metastatic disease (1).

Model structure

A three-state, partitioned survival cost-effectiveness model was developed in Microsoft Excel®, based on guidance from the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 19 (56). An economic modelling expert agreed that the model structure was appropriate as it directly captures the clinically meaningful primary and secondary time-to-event outcomes from the ARAMIS clinical trial (57). This model structure is fully aligned with the primary objectives of treatment in nmCRPC: avoiding disease progression to metastatic CRPC and its associated burden on quality of life and prolonging life. The health states selected are typical of modelling in oncology and have been used in previous NICE prostate cancer technology appraisals (58-61). This model contains the three most relevant disease-related health states from a patient, clinician and National Health Service (NHS) perspective (as shown in Figure 12):

- nmCRPC, metastatic progression-free
- mCRPC, metastatic progressed
- Dead

Although clinical experts suggested that the three-state partitioned survival model may oversimplify the metastatic disease progression state, they agreed that this model structure is appropriate given the availability of trial and publicly accessible data, where splitting the mCRPC state by line of therapies will introduce significant uncertainty to the cost-effectiveness model given that data will be based on external trials (3). This is also in line with the committee and Evidence Review Group's (ERG)

opinion in TA580, where they expressed concerns about the proposed sequence and transition estimates between the progressed states of the company's model (2). However, to overcome this for the model submitted as part of this appraisal, the costs and utility associated with each subsequent treatment line is accounted for within the mCRPC health state (3) (please refer to Sections B.3.4 and B.3.5. for more details).

Parametric survival models based on the ARAMIS primary endpoint (metastasis-free survival [MFS]) and one of the key secondary endpoints (overall survival [OS]) were used directly to estimate the proportion of patients in the nmCRPC, metastatic castration-resistant prostate cancer (mCRPC) and dead health states over time, where nmCRPC = MFS, mCRPC = OS − MFS, and dead = 1 − OS.

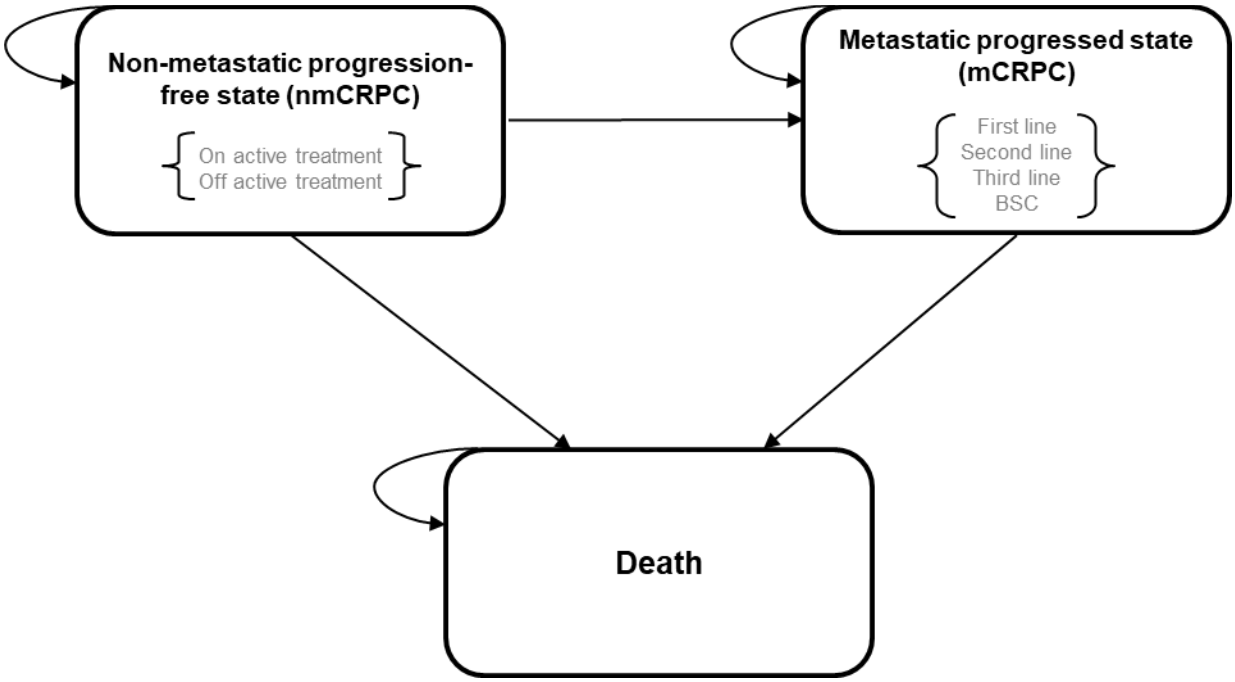
All patients enter the model at the nmCRPC health state without metastasis and are at risk of metastatic progression or death, where death is an 'absorbing state'. Upon metastatic progression, patients move to the mCRPC health state and continue to be at risk of death. The metastatic progression-free health state is designed to capture the relatively higher quality of life (QoL) while the disease is controlled prior to progression and patients are receiving benefit from an active treatment. The metastatic progressed disease health state is designed to capture the relatively poor QoL following disease progression and prior to death. The model, therefore, captures the changes in QoL between pre- and post-metastatic progression through the relevant health states:

- Metastatic progression-free: patients' disease is in a stable or responding state and not actively progressed to metastases. Patients in this state are assumed to incur costs associated with treatment acquisition, treatment administration, medical management of the condition and the management of Grade 3/4 adverse events (AEs) and all grades of symptomatic skeletal events (SSEs). For the darolutamide + ADT arm, the nmCRPC health state is further partitioned into active treatment and no active treatment, based on modelled time on treatment (ToT) where patients discontinue treatment upon metastatic progression. ToT was bounded by MFS in line with the SmPC where darolutamide is given "until

radiographic disease progression as assessed by conventional imaging (CT, bone scan, MRI) by blinded central review, unacceptable toxicity or withdrawal" (Appendix C). In line with current UK clinical practice, background ADT is still used in the no active treatment phase within the nmCRPC health state for the darolutamide + ADT arm (3). Metastatic progression-free patients also experience a higher utility compared with patients with metastatic progressed disease

- Metastatic progressed: patients' disease is assumed to have progressed to metastases and patients are assumed to have moved onto subsequent treatment, if eligible. In this health state, patients are assumed to receive first-line, second-line and third-line treatments upon progression, as displayed in Figure 12. The subsequent treatment distributions for each line were sourced from the clinical validation advisory board to accurately reflect current clinical practice in the UK (3). In this health state, acquisition and administration costs of subsequent therapies and costs of disease management were captured (see Section B.3.5 for more details). Given that this health state is associated with a lower QoL, and to accurately capture the utility at each line of therapy, a weighted average was applied based on the time spent in each line of therapy in the metastatic progression states (see Section B.3.4 for more details)
- Dead: this is an absorbing state where a palliative care cost is applied upon death

Figure 12: Model structure



Key: mCRPC, metastatic castration-resistant prostate cancer; nmCRPC, non-metastatic castration-resistant prostate cancer; BSC, best supportive care.

Features of the economic analysis

The economic analyses were conducted from an NHS and Personal Social Services perspective in England and Wales. The model uses a 28-day cycle length, with a half-cycle correction applied, and a 27-year time horizon. This aligns with the maximum life expectancy of the cohort predicted by parametric survival analysis. The impact on model results of selecting a different time horizon is explored in sensitivity analysis. A discount rate of 3.5% per annum was applied for costs and benefits. The perspective chosen, time horizon assessed and the discount rates used are all in line with the NICE reference case (62).

There has been one prior NICE technology appraisal for the treatment of non-metastatic prostate cancer (enzalutamide for nmHRPC, TA580) (2), which is considered a relevant comparative precedent. The features of the de novo analysis compared with the features of the model appraised in TA580 (2) are reported in Table 21.

Table 21: Features of the economic analysis

Factor	TA580(2)	Current appraisal	Justification
	Chosen values	**Chosen values**	
Time horizon	20 years	27 years	A lifetime horizon was used (27 years, given the mean patient age in the cost-effectiveness model based on the ARAMIS trial is 73.6 years and assuming a maximum life expectancy of 100). This is considered to be adequately long that the majority of patients would have died by the end of the model time horizon, so that the model is able to capture relevant benefits and costs for the darolutamide and ADT arms in line with the NICE reference case (62).
Cycle length	30-day	28-day	Based on the treatment cycle of darolutamide.
Health states	Metastatic progression-free, death and metastatic progressed disease further divided into three sub-states: • Docetaxel not yet indicated • Docetaxel indicated • Post-docetaxel	Metastatic progression-free, metastatic progressed and death	Reflects the aim of treatment in nmCRPC, i.e. avoiding metastases and prolonging life. The sequencing semi-Markov model structure in TA580 was criticised for its complexity and mismatch with the data available from PROSPER i.e. overall survival data had to be split into pre- and post-metastatic progression, breaking randomisation and potentially introducing bias; also, because collection of the MFS primary endpoint ceased when this endpoint was met, a different endpoint had to be used as a

Factor	TA580(2)	Current appraisal	Justification
	Chosen values	Chosen values	
			proxy for MFS to split the OS data introducing additional uncertainty. To overcome the complications introduced by adopting a sequencing structure, a three-state partitioned survival model was chosen with in-built granularity to account for the distribution of subsequent treatment lines, their costs and the utility associated with each treatment line in the mCRPC state.
Comparator	ADT	ADT	In line with the current clinical practice in NHS England and the May 2019 published NICE guideline on the treatment and management of high-risk localized or locally advanced prostate cancer [NG131] (33) as well as the NICE final scope (63).
Source of utilities	EQ-5D data in PROSPER for the non-metastatic state and the first progressed state of the model	nmCRPC: EQ-5D-3L data from ARAMIS mCRPC: A weighted average utility estimates based on the time spent in each line of therapy in the metastatic	Utility values for the nmCRPC state were derived from EQ-5D-3L data collected in ARAMIS, in line with the NICE reference case (62). Utility values for mCRPC from ARAMIS were based on a small sample size and were not reflective of the whole mCRPC health state, as most data were collected in the

Factor	TA580(2)	Current appraisal	Justification
	Chosen values	**Chosen values**	
	Other progressed state utility values came from PREVAIL and AFFIRM trials' EQ-5D data (2). End-of-life utility applied for 3 months prior to death.	progressed disease states (2, 58)	early stage of mCRPC. As such, the utility value for the mCRPC state was estimated from TA377 (58), TA580 (2) and SMC2195 (64), where a weighted average utility was calculated based on the time spent in each line of therapies in the metastatic disease progression state (as detailed in section B.3.4.).
Source of costs	NHS reference costs (65)	**Drug costs:** MIMS (66) and eMIT (generic) (67) **Other costs:** NHS reference costs (65) (administration, monitoring and adverse event costs) and PSSRU (68) (administration, monitoring and palliative care costs)	**Drug costs:** The public list price of the treatments should be used, in line with the NICE reference case (62) **Other costs:** Consistent with the NICE reference case (resource use costs should be valued using prices that are relevant to the NHS) (65)
Half-cycle correction applied?	Yes	Yes	Consistency with NICE reference case (62)

Factor	TA580(2)	Current appraisal	Justification
	Chosen values	**Chosen values**	
Health effects measure	QALYs	QALYs	Consistency with NICE reference case (62)
Discount rates	3.5%	3.5%	Consistency with NICE reference case (62)
Perspective	NHS/PSS	NHS/PSS	Consistency with NICE reference case (62)
Key: ADT, androgen deprivation therapy; eMIT, drugs and pharmaceutical electronic market information tool; EQ-5D-3L, 3-level EQ-5D; MIMS, Monthly Index of Medical Specialities; NHS, National Health Service; NICE; National Institute for Health and Care Excellence; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted life year; nmCRPC, non-metastatic castration-resistant prostate cancer; mCRPC, metastatic castration-resistant prostate cancer.			

Intervention technology

Darolutamide treatment scheduling is implemented in the model at a dose of 600 mg (two 300 mg tablets) twice daily, with patients receiving ADT as background therapy. This is in line with the ARAMIS trial and expected licence for darolutamide. Darolutamide is administrated until metastatic disease progression or unacceptable toxicity, where ToT data from ARAMIS are used to capture how long patients stay on darolutamide in the model (see Section B.3.3 for more details).

Comparators

As discussed in Section B.1.3, when prostate cancer remains localized, ADT is the only available therapy. Although ADTs are known to decrease PSA levels, resistance is experienced in almost all patients over time. There are currently no nmCRPC-specific treatments recommended in the UK (33); therefore, ADTs were considered as the only relevant comparator for the model. This is in line with the NICE final scope (63), the current clinical practice in England and the May 2019 published NICE guideline on the treatment and management of high-risk localized or locally advanced prostate cancer (NG131) (33). Based on clinical opinion from the validation advisory board(3) and in line with the ARAMIS trial protocol, a blended basket of common ADT treatments – including leuprorelin (40%), goserelin (30%), triptorelin (20%) and buserelin (10%) – was used to represent the ADT arm.(3) In line with the clinical experts' opinion in the validation meeting (3), no background steroid treatments are used with ADT.

In the ARAMIS study, patients in both treatment arms remained on ADT throughout the trial duration. Therefore, patients in both arms received ADT across the entire model time horizon. This is further detailed in Section B.3.5.

B.3.3. Clinical parameters and variables

The pivotal ARAMIS trial (3 September 2018 data cut) provided the key efficacy, safety and QoL data for the darolutamide and ADT arms in the model. The model clinical inputs, based on the ARAMIS trial, included:

- MFS and OS patient-level data used for fitting parametric survival models for the darolutamide and ADT arms
- ToT patient-level data used to further partition the darolutamide MFS state into active treatment and no active treatment
- SSE and AE rates for the darolutamide and ADT arms (detailed in Section B.3.4)
- Three-level EQ-5D (EQ-5D-3L) patient-level data used for deriving health utility values and fitting regression models to estimate health utilities for the nmCRPC and mCRPC health states (detailed in Section B.3.4)
- Type and distribution of subsequent treatments in the mCRPC health state (detailed in Section B.3.5)
- Baseline patient characteristics including age, weight, height and body surface area

Baseline scans from the ARAMIS trial were reanalysed by blinded central imaging review (BCIR). This identified patients who had metastases at baseline that had not been identified at the time of randomization by the investigators (5.2% of the darolutamide + ADT arm and 7.0% of the placebo arm). Therefore, analyses affected by this (MFS and health utilities) were all conducted using two alternative censoring rules. Both analyses were based on the ARAMIS intention-to-treat (ITT) population, including all patients enrolled in the study and analysed according to the groups they were randomized to. A modified ITT analysis removing the baseline metastases patients (as identified by BCIR) was deemed inappropriate as it would break the randomization of the ARAMIS trial; therefore, this was not performed. The alternative analyses were defined as follows:

- BMC = baseline metastases censored at Day 0
- BME = baseline metastases counted as events at Day 0

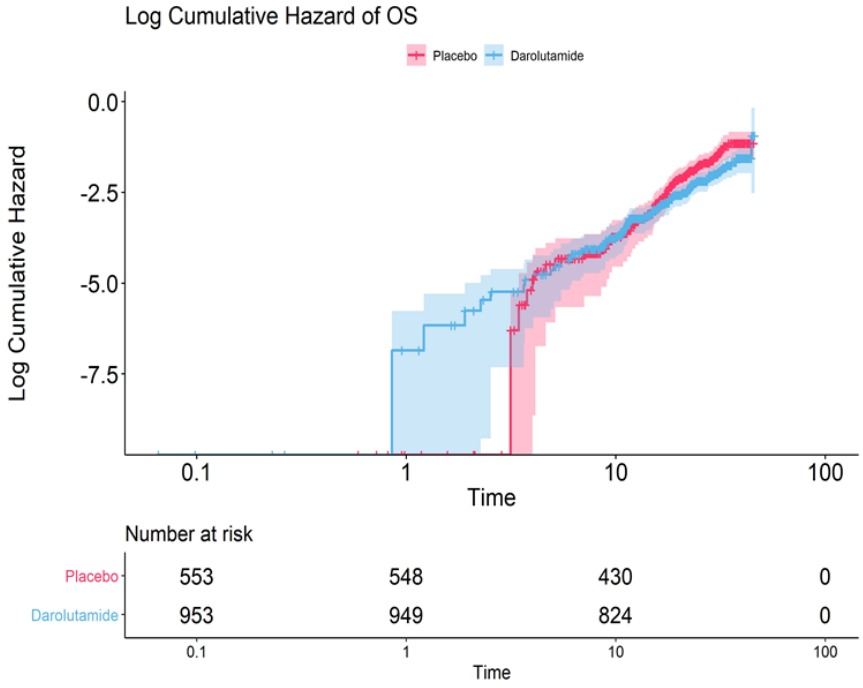
The model base case used the BMC analysis because:

- The relevant patient population for the model is patients with high-risk nmCRPC. Therefore, by definition, patients with confirmed baseline metastases should not contribute to the analysis, or the impact of these patients should be kept to a minimum (e.g., in order to preserve randomization)
- The primary MFS analysis in the ARAMIS trial was based on metastases identified by BCIR (not by investigators), and the exclusion criteria for ARAMIS prohibited patients with metastases at baseline

The above rational were validated and accepted by clinical experts at the advisory board, where it was agreed that although in clinical practice some metastatic patients would be missed, for the purpose of the cost-effectiveness analyses it is more conservative to censor patients with metastasizes at baselines to avoid confounding the analyses (3). As such, the BME analyses for MFS extrapolations and utilities are included in the model as alternative scenarios, and the Kaplan–Meier and extrapolations are displayed in Appendix K.

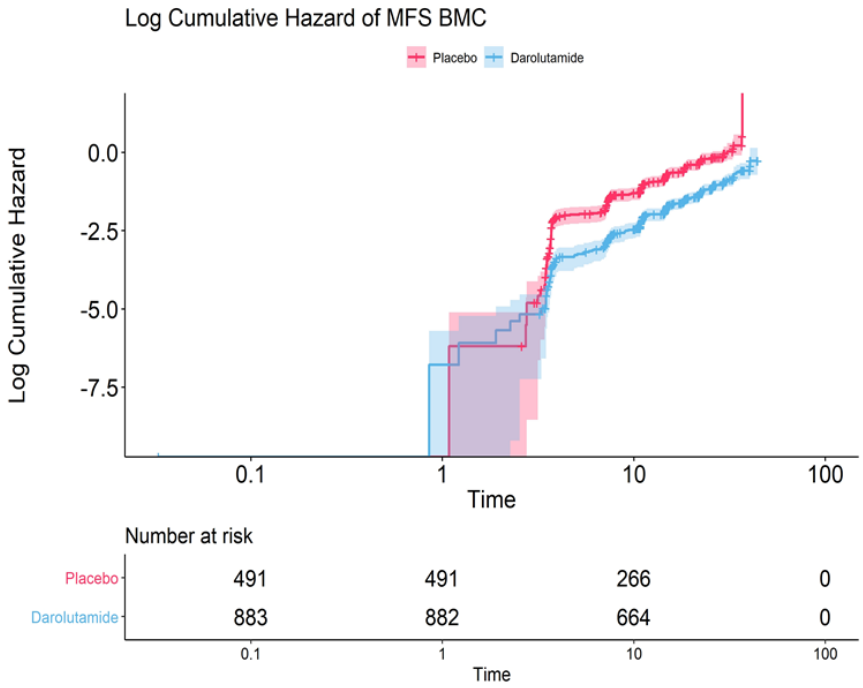
Parametric survival curves were fitted separately to the darolutamide and placebo arms, using ARAMIS patient-level data, in order to extrapolate beyond the trial follow-up period. This is in line with NICE DSU TSD 14 (69), which considers separate curve fits to be the most appropriate approach when patient-level data are available and in the event where the proportional hazard assumption does not hold. As shown in Figure 13 and Figure 14, the log-cumulative hazard curves from the ARAMIS trial for the OS and BMC MFS cross at various timepoints, supporting the approach of using separate parametric models for the ADT and the darolutamide + ADT arms.

Figure 13: ARAMIS – OS log cumulative hazard



Key: OS, overall survival.

Figure 14: ARAMIS – MFS BMC log cumulative hazard



Key: BMC, baseline metastases censored at Day 0; MFS, metastasis-free survival.

All parametric survival curves were based on the ITT population from the ARAMIS trial. Standard parametric survival curve fitting was conducted in line with NICE DSU TSD 14 (69). All fitted standard parametric curves including exponential, log-normal, log-logistic, Gompertz, Weibull and generalized gamma were considered, compared and assessed using the below goodness-of-fit criteria:

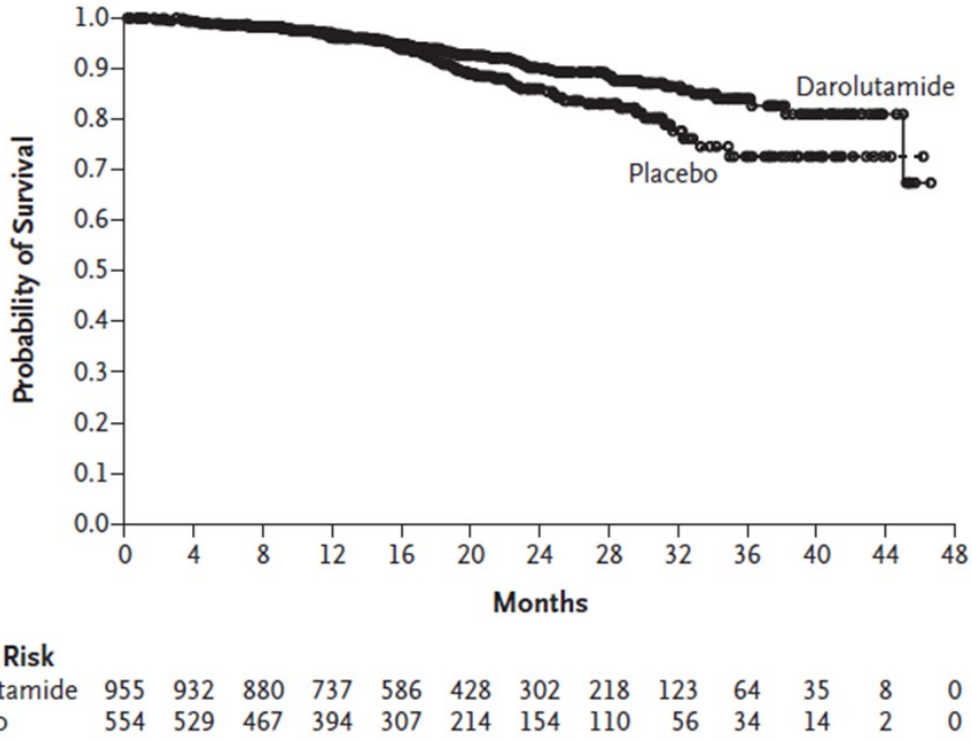
- Akaike information criterion (AIC) and Bayesian information criterion (BIC) – smaller AIC/BIC values indicate a better statistical fit. In general, models with a difference in AIC and BIC of less than 5 are assumed to be of equal statistical fit
- A visual inspection of the fitted curves – the fitted parametric survival model curves were overlaid on the Kaplan–Meier curves to assess how closely the model data matched the observed non-parametric estimates of survival
- Clinical experts' opinion and validation of extrapolated survival curves beyond the trial period – Bayer conducted a clinical validation meeting on 4 February 2020, consisting of nine practicing oncologists and one urologist (3).

Based on recommendations from NICE DSU TSD 14,(69) the same type of parametric survival curves were chosen for both treatment arms (e.g., if Weibull was chosen for modelling OS for darolutamide, then Weibull was also used to model OS for the ADT arm).

Overall survival

Due to incomplete Kaplan–Meier data, parametric survival models were used to estimate OS for the darolutamide and ADT arms of the model, fitted using patient-level data from ARAMIS. The 3 September 2018 data cut was used in the analysis, at which point there had been 78 OS events in the darolutamide + ADT arm and 58 OS events in the placebo arm. Median survival had not been reached at the time of the data cut for either arm (Figure 15).

Figure 15: ARAMIS OS Kaplan–Meier (3 September 2018 data cut) (70)



Key: OS, overall survival.

Figure 16 and Figure 17 present the six parametric curves fitted to the OS patient-level data for darolutamide and ADT, respectively. The AIC/BIC statistics are presented in Table 22.

Considering both AIC/BIC statistics and visual fit to the observed Kaplan–Meier data, log-logistic, log-normal and Weibull were the best-fitting models for both arms; these had the lowest AIC and BIC values and all fitted the observed Kaplan–Meier data well within the trial follow-up period.

Of the best-fitting models, the Weibull model was selected for the model base case for both arms as it was deemed the most appropriate curve selection and the most conservative estimate of absolute OS for the darolutamide + ADT and ADT arms. This was further validated by clinical experts at the validation meeting, where the Weibull curve was considered to be the most plausible curve for both arms, i.e. all experts agreed the predicted survival of the Weibull model at key time points (e.g. at

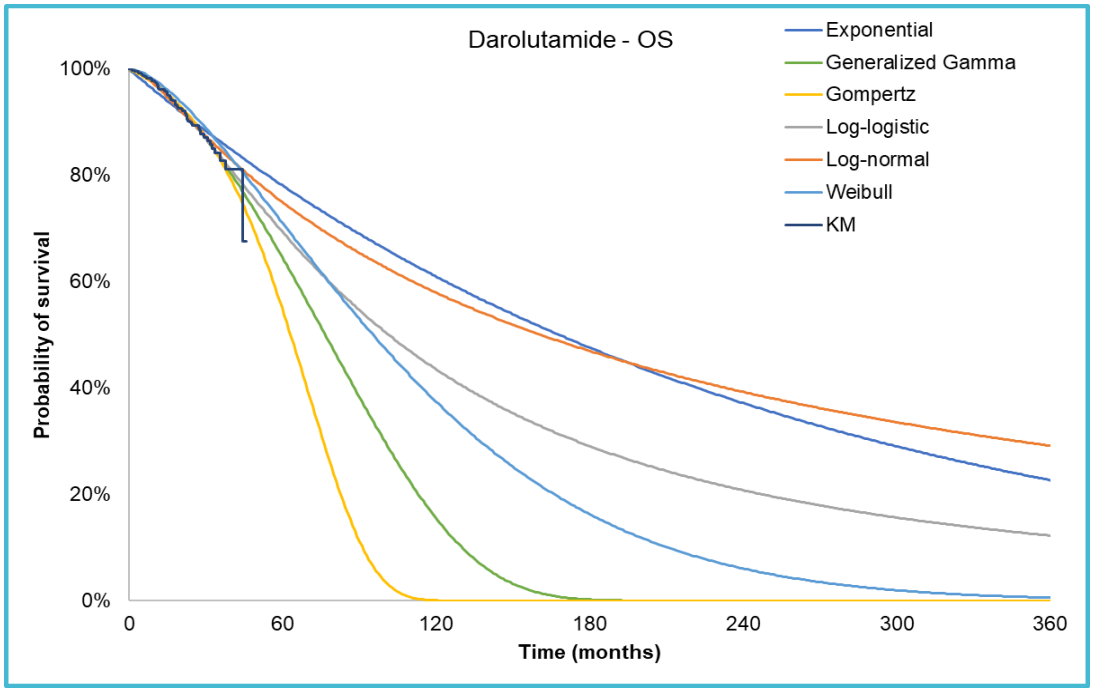
5 years, 10 years, 15 years, etc.) in the ADT arm closely matches what is currently observed in clinical practice, while the predicted survival in the darolutamide + ADT arm is in line with what the experts expect (3). The log-logistic and log-normal curves tended to have flat tails (decreasing mortality risk over time), which may over estimate long-term survival. Alternative curves options were explored in scenario analyses.

With a lifetime time horizon and relatively immature OS evidence from the ARAMIS trial, one of the key uncertainties of the model is the extrapolation of long-term OS beyond the trial follow-up period, with wide variability among potential extrapolations contributing to uncertainty. General population mortality, based on national life tables (71), was used in the model to ensure that in any model cycle, the modelled mortality for all treatment arms was equal to or greater than the age-matched general population. Furthermore, given uncertainties in mortality risk and treatment effect of darolutamide versus ADT, beyond the ARAMIS trial follow-up period, the model included the functionality to assume the ADT arm has the same mortality risk as the darolutamide + ADT arm after a user-defined cut-off time. Clinical expert opinion was that it would be overly conservative to assume an equal mortality risk for both arms after trial follow-up in the model base case, and that a survival benefit for darolutamide could be observed over a number of years (3). As results from the latest AMARIS data cut (15 November 2019) (72) have shown a significant improvement in OS for patients receiving darolutamide + ADT compared with ADT, no assumption of equal mortality is considered in the base case, but an assumption of equal efficacy at 8.7 years is applied in scenario analysis (see Section B.3.8). The choice of cut-off is in line with ERG's suggested modelling approach from TA580 in which it was assumed the effect of enzalutamide relative to ADT improves up to 8.7 years, tapers between 8.7 and 17 years (i.e. equal risk of death at 17 years), and reverses after that. Our model takes the simplifying approach of assuming an equal risk of death right from the cut-off point, without modelling the taper off and reversal period of the relative effect. This is likely to be conservative given the long taper off period suggested in TA580 (i.e. 8.3 years) and the relatively lower proportion of the cohort still alive past the reversal point (i.e. during the 10 years of the remaining

lifetime horizon), but serves as a good way to explore a more conservative stance in relation to the uncertainty in the extrapolated relative mortality risk from ARAMIS.

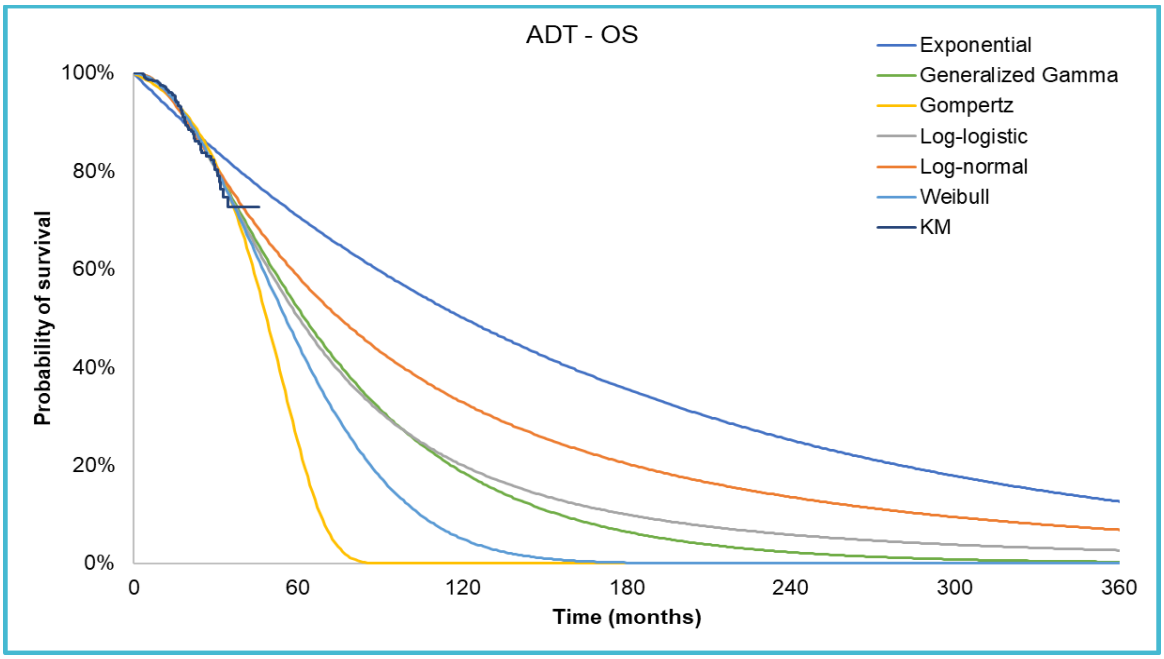
The final base case OS curves for darolutamide and ADT are presented in Figure 18. *Note: The updated cost-effectiveness results, using analysis from this latest data cut, will be provided to NICE at the earliest available opportunity.*

Figure 16: Parametric OS models for the darolutamide + ADT arm



Key: ADT, androgen deprivation therapy; KM, Kaplan–Meier; OS, overall survival.

Figure 17: Parametric OS models for the ADT arm



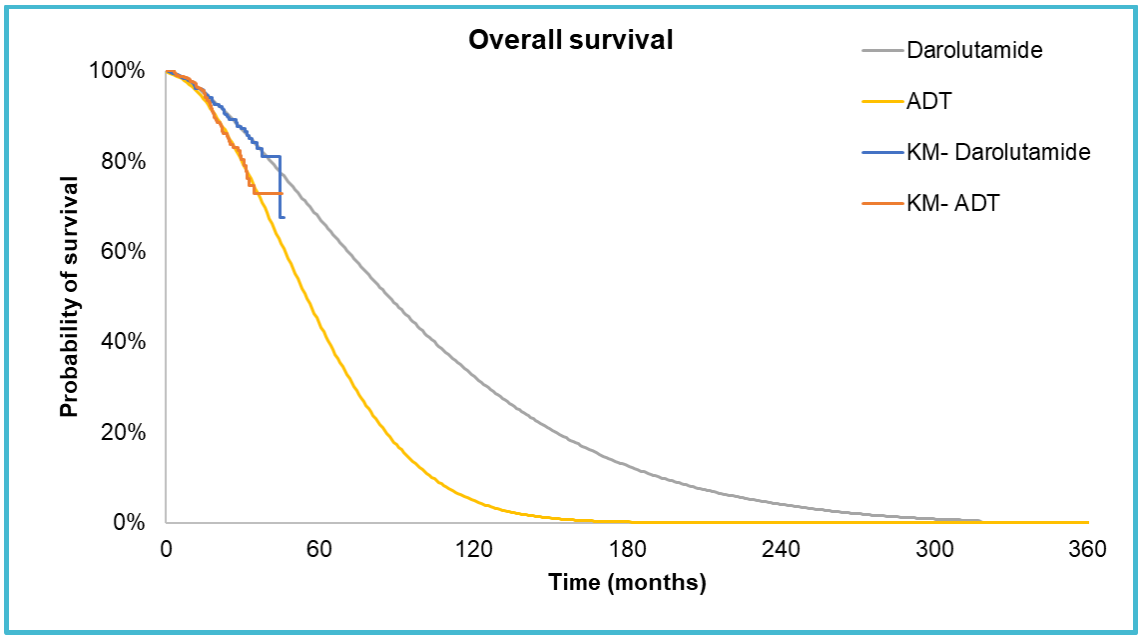
Key: ADT, androgen deprivation therapy; KM, Kaplan–Meier; OS, overall survival.

Table 22: AIC and BIC values for separately fitted parametric survival model curves for OS

Distribution	Darolutamide		ADT	
	AIC	BIC	AIC	BIC
Exponential	1,547.6	1,552.4	1,112.8	1,117.1
Generalized gamma	1,536.6	1,551.2	1,088.4	1,101.3
Gompertz	1,537.2	1,546.9	1,094.9	1,103.6
Log-logistic	1,534.8	1,544.6	1,086.4	1,095.0
Log-normal	1,538.1	1,547.9	1,087.2	1,095.9
Weibull	1,534.7	1,544.4	1,087.1	1,095.7

Key: ADT, androgen deprivation therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Figure 18: Selected OS curve (Weibull) for the darolutamide and ADT arms

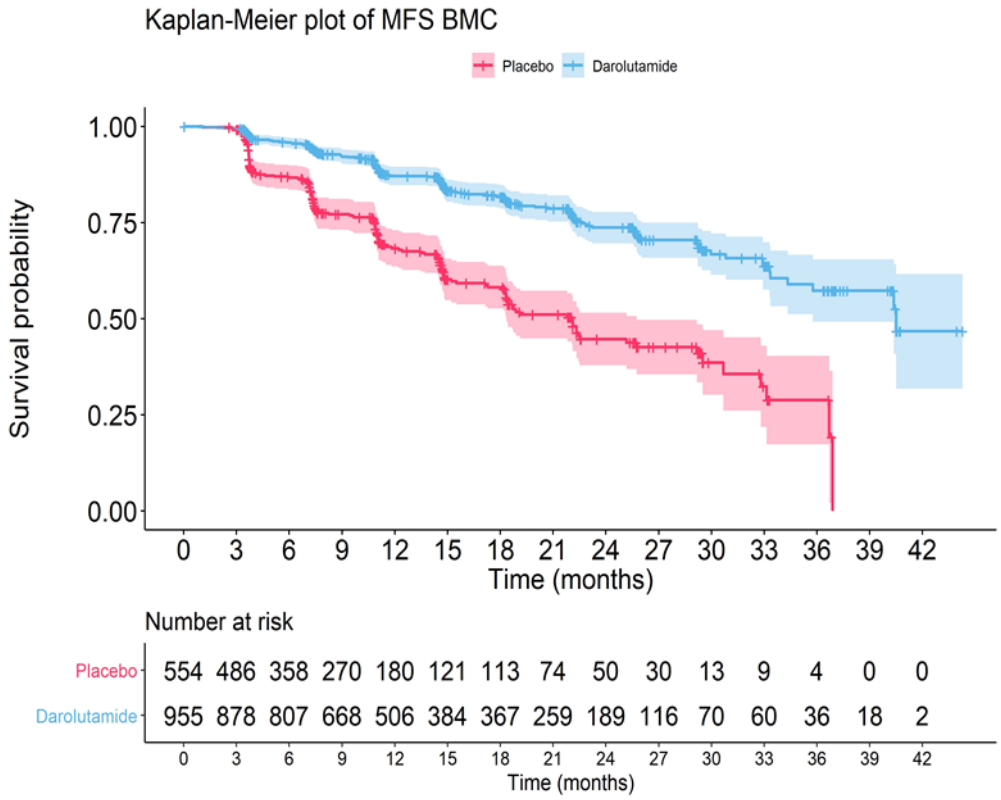


Key: ADT, androgen deprivation therapy; KM, Kaplan–Meier; OS, overall survival.

Metastasis-free survival

Due to incomplete data, MFS parametric survival curves (both MFS BMC and MFS BME) for the darolutamide and ADT arms were fitted using patient-level data from ARAMIS to extrapolate MFS over time. The 3 September 2018 data cut was used in the analysis, at which point there had been 171 MFS BMC events in the darolutamide + ADT arm and 177 MFS BMC events in the placebo arm. Figure 19 presents the MFS BMC Kaplan–Meier data based on the ARAMIS trial. MSF BME analyses are displayed in Appendix K.

Figure 19: ARAMIS MFS BMC Kaplan–Meier (3 September 2018 data cut) (70)



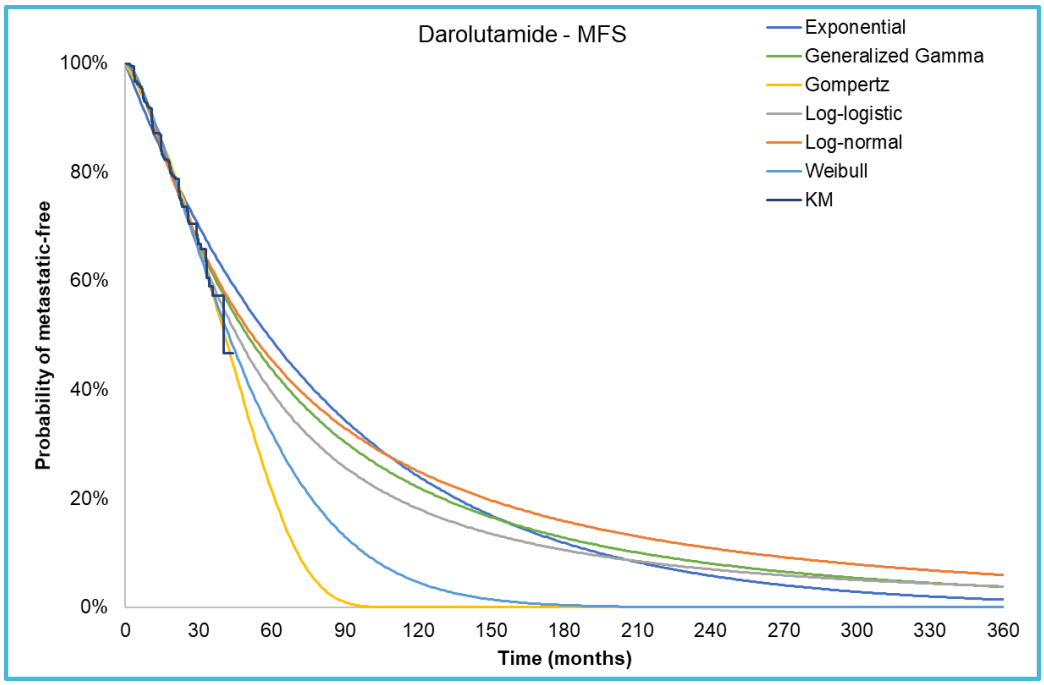
Key: BMC, baseline metastases censored at Day 0; MFS, metastasis-free survival.

Figure 20 and Figure 21 present the six parametric curves for MFS BMC fitted to the patient-level data for darolutamide and ADT, respectively. The AIC/BIC statistics are presented in Table 23. As discussed above, the BMC analysis was used in the model base case, with the BME analysis explored as an additional scenario analysis.

Considering AIC/BIC statistics and visual fit to the observed Kaplan–Meier data, generalized gamma, log-logistic, log-normal and Weibull were the best-fitting models for both arms, as they all fitted the observed Kaplan–Meier data well within the trial follow-up period and had similarly low AIC and BIC. Among the best-fitting models, Weibull was used in the base case as other best-fitting models caused the extrapolated MFS to be higher than the extrapolated OS for the same treatment arm when OS was extrapolated using the Weibull distribution. The Weibull model also gave the most conservative estimate of absolute MFS for the darolutamide + ADT and ADT arms among the best-fitting models. In the validation advisory board clinical

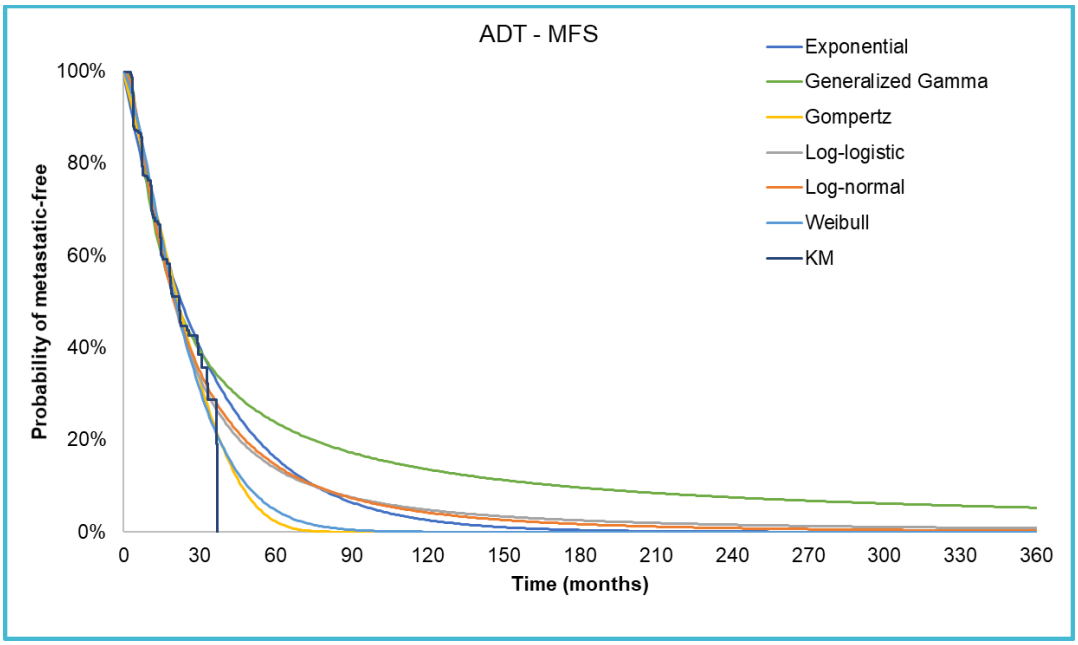
experts agreed that the Weibull is the most plausible and conservative distribution for both arms and in line with what is currently observed in clinical practice in relation to the ADT arm (3). Alternative curves options were explored in scenario analyses. The final base case MFS BMC for darolutamide and ADT is presented in Figure 22.

Figure 20: Parametric survival models for the darolutamide + ADT arm: MFS BMC analysis



Key: ADT, androgen deprivation therapy; BMC, baseline metastases censored at Day 0; KM, Kaplan–Meier; MFS, metastasis-free survival.

Figure 21: Parametric survival models for the ADT arm: MFS BMC analysis

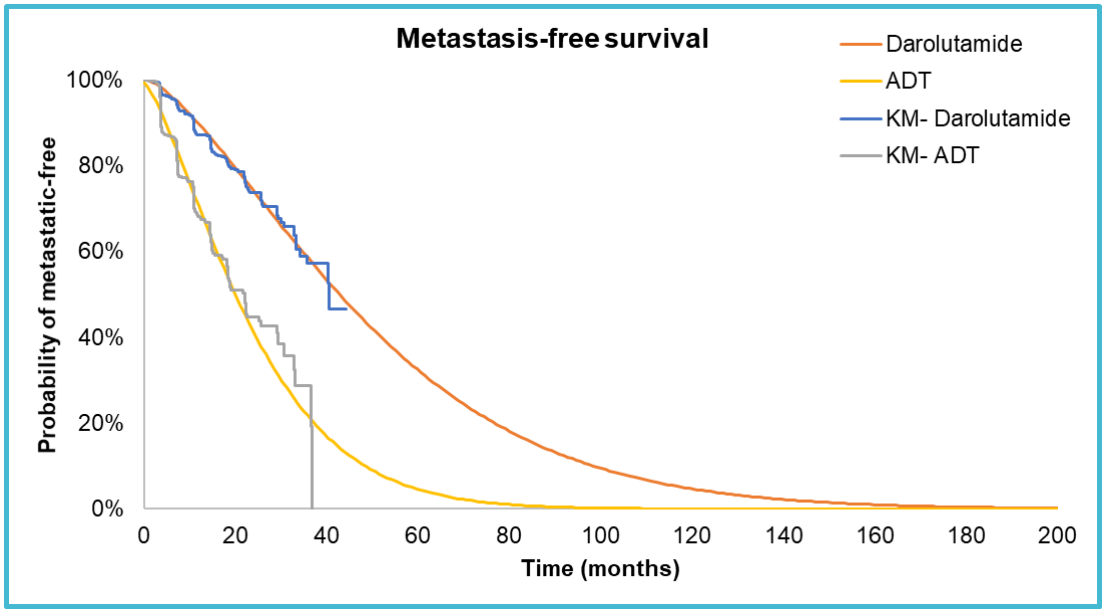


Key: ADT, androgen deprivation therapy; BMC, baseline metastases censored at Day 0; KM, Kaplan–Meier; MFS, metastasis-free survival.

Table 23: AIC and BIC values for separately fitted parametric survival model curves: MFS BMC analysis

Distribution	Darolutamide		ADT	
	AIC	BIC	AIC	BIC
Exponential	3,029.3	3,034.2	2,801.2	2,805.5
Generalized gamma	3,001.4	3,015.9	2,752.8	2,765.7
Gompertz	3,015.6	3,025.4	2,794.3	2,802.9
Log-logistic	3,002.6	3,012.3	2,769.5	2,778.1
Log-normal	2,999.5	3,009.2	2,756.7	2,765.4
Weibull	3,004.1	3,013.8	2,777.9	2,786.6
Key: ADT, androgen deprivation therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; BMC, baseline metastases censored at Day 0; MFS, metastasis-free survival.				

Figure 22: Selected MFS BMC curves (Weibull) for the darolutamide and ADT arms



Key: ADT, androgen deprivation therapy; BMC, baseline metastases censored at Day 0; KM, Kaplan–Meier; MFS, metastasis-free survival.

Time on treatment

Darolutamide

Although more complete than PFS and OS, ARAMIS darolutamide ToT data were still incomplete. Therefore, parametric survival curves were fitted using ARAMIS patient-level data in order to extrapolate how long patients were treated with darolutamide for, where ToT was defined as the time from the start until the end of the study treatment period; patients were censored if they remained on treatment at the cut-off date. The 3 September 2018 data cut was used in the analysis, at which point [redacted] of the [redacted] patients randomized to the darolutamide + ADT arm had stopped receiving treatment. *Note: More mature ToT data from the final data cut-off (15th November 2019) will be submitted as soon as it becomes available.*

Figure 23 presents the six parametric curves fitted to the ToT patient-level data for darolutamide. The AIC/BIC statistics are presented in Table 24. Considering the AIC/BIC statistics and visual fit to the observed Kaplan–Meier data, the exponential,

generalized gamma, Gompertz, log-logistic and Weibull models all fit the observed Kaplan–Meier data well within the trial follow-up period. Among the best-fitting models, Gompertz was used as the base case model. In the clinical validation meeting, one clinical expert shared that, based on their clinical experience, it may be possible for a very small percentage of patients to still be on darolutamide at 15 years (3). Moreover, another expert argued it would be best to choose the Weibull for consistency between other endpoints, specifically MFS. However, the majority of clinical experts commented that the best model lies between Weibull and Gompertz, but supported the use of Gompertz in the base case. The Weibull curve, along with other curve options, were explored in scenario analyses.

The base case ToT for darolutamide is presented in Figure 24.

Figure 23: Parametric survival models for the darolutamide + ADT arm: ToT

Key: ADT, androgen deprivation therapy; KM, Kaplan–Meier; ToT, time on treatment.

Table 24: AIC and BIC values for separately fitted parametric survival model curves for ToT

Distribution	Darolutamide	
	AIC	BIC
Exponential	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; ToT, time on treatment.		

Figure 24: Selected ToT curves for the darolutamide + ADT arm

Key: ADT, androgen deprivation therapy; KM, Kaplan–Meier; ToT, time on treatment.

Androgen deprivation therapy

For both the ADT and darolutamide + ADT model arms, based on clinical practice, background ADT was applied for the entire model horizon. This assumption was further validated and accepted by clinical experts at the validation meeting (3) and is also in line with the assumptions made in the NICE appraisal of enzalutamide in nmHRPC (TA580) (2).

B.3.4. Measurement and valuation of health effects

Health-related quality of life data from clinical trials

Health-related quality of life (HRQL) data were collected in the ARAMIS trial using the EQ-5D-3L, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Prostate Cancer (EORTC-QLQ-PR25), the Functional Assessment of Cancer Therapy-General (FACT-G), the FACT-P (prostate) and the FACT-P Prostate Cancer Subscale (PCS). There were no available algorithms mapping the EORTC-QLQ-PR25 or the FACT-P PCS to EQ-5D utilities. While there are algorithms mapping the FACT-G and FACT-P to EQ-5D utilities, no further information would have been gained from any mapping exercises as there were a similar number of observations for these questionnaires and the EQ-5D questionnaire as they were collected at screening, Visit 1, Visit 4 and at the end of study treatment visit. Visit 4 occurred 16 weeks (±7 days) from the start of the study. Table 25 details the number of observations in each arm per visit.

Table 25: Summary of the number of observations in each visit for the EQ-5D questionnaire (70)

Summary variables	**Number of observations** **Number of patients** **Mean (SD)** **Median (Range)**		
	Darolutamide N=955	Placebo N=554	All N=1,509
All	1,933 943	1,188 550	3,121 1,493

Summary variables	**Number of observations** **Number of patients** **Mean (SD)** **Median (Range)**		
	Darolutamide N=955	Placebo N=554	All N=1,509
	0.82 (0.193) 0.848 (-0.291, 1)	0.805 (0.219) 0.814 (-0.19, 1)	0.814 (0.203) 0.848 (-0.291, 1)
Visit			
Screening	24 24 0.819 (0.228) 0.796 (0.082, 1)	14 14 0.774 (0.275) 0.83 (0.258, 1)	38 38 0.807 (0.235) 0.812 (0.082, 1)
Visit 1	927 927 0.828 (0.182) 0.848 (-0.166, 1)	544 544 0.824 (0.194) 0.848 (-0.19, 1)	1471 1471 0.826 (0.186) 0.848 (-0.19, 1)
Visit 4	876 876 0.819 (0.191) 0.848 (-0.291, 1)	494 494 0.806 (0.213) 0.813 (-0.181, 1)	1370 1370 0.814 (0.2) 0.814 (-0.291, 1)
End of study treatment	106 106 0.752 (0.266) 0.796 (-0.108, 1)	136 136 0.733 (0.302) 0.796 (-0.166, 1)	242 242 0.742 (0.286) 0.796 (-0.166, 1)
Health state (BMC)			
Before metastasis	1,752 941 0.824 (0.187) 0.848 (-0.291, 1)	935 537 0.816 (0.204) 0.848 (-0.19, 1)	2,687 1,478 0.821 (0.193) 0.848 (-0.291, 1)
After metastasis	63 58 0.759 (0.23) 0.796 (-0.016, 1)	105 86 0.731 (0.298) 0.796 (-0.166, 1)	168 144 0.741 (0.274) 0.796 (-0.166, 1)

Key: BMC, Baseline metastasis censored; SD, standard deviation.

The EQ-5D is a standardized and validated generic instrument; the preference elicitation is based on a time trade-off algorithm, which corresponds to the NICE

reference case (62, 73). Therefore, utility values were estimated from the EQ-5D-3L responses using the UK time trade-off method described in Dolan et al. Patients who answered '1' to all five dimensions (e.g., 11111) have a 'perfect health' utility value of 1. For dimensions that a patient answered '2' or '3' (i.e. has some problems or extreme problems), a utility decrement was applied to the overall utility value as shown in Equation 1 below.

Equation 1: Calculation of EQ-5D utility value (UK tariff)

$$\text{EQ} - \text{5D utility value} = 1 - 0.069\,\text{MO2} - 0.314\,\text{MO3} - 0.104\,\text{SC2} - 0.214\,\text{SC3} - 0.036\,\text{UA2} - 0.094\,\text{UA3} - 0.123\,\text{PD2} - 0.386\,\text{PD3} - 0.071\,\text{AD2} - 0.236\,\text{AD3} - 0.081\,\text{N2} - 0.269\,\text{N3}$$

Key: AD, anxiety/depression; MO, mobility; N2, one or more questions reported as a 2 or 3; N3, one or more questions answered with a 3; PD, pain/discomfort; SC, self-care; UA, usual activity.
Note: The number following the codes indicates a Level 2 or Level 3 response.

Univariate mixed-effects models were fitted for each baseline utility and showed that age and health state were all statistically significant covariates (Table 26). Therefore, each was included in the final mixed effect models.

Table 26: Summary of univariate mixed-effects models

Coefficient	Parameter value	SE	p-value
Baseline utility	0.685	0.024	<0.001
Age	-0.002	0.001	0.002
Treatment: darolutamide	0.012	0.010	0.225
Health state (BMC): after	-0.073	0.013	<0.001
Health state (BME): after	-0.047	0.011	<0.001
Key: BME, baseline metastasis as event at Day 0; BMC, baseline metastasis censored at Day 0; SE, standard error.			

The linear mixed-effect models were fitted to the ARAMIS EQ-5D-3L data, including a random effect for 'patient' to capture the correlations between repeated assessments. Where progression is defined according to the BMC central reviewer rule, two utility regression models were analysed:

- Pooled BMC: where observations from both arms were pooled together
  - Utility ~ baseline utility + age + health state (defined according to the BMC central review rule)
- Separate BMC: where observations from both arms were used separately
  - Utility ~ baseline utility + age + treatment arm + health state (defined according to the BMC central review rule)

The base case pooled BMC mixed-effects model results are shown in Table 27, which indicate that after controlling for other covariates, the mCRPC health state utility was 0.064 lower than the nmCRPC health state utility, based on the EQ-5D data collected in the ARAMIS trial. The separate BMC mixed-effects model summarized in Table 28 includes health state BMC and controls for the treatment arm, as well as baseline utility and baseline age of the patients that contributed a utility value. All the variables were statistically significant except age, which was on the threshold of significance, and treatment, which is expected given that little difference was observed between treatment arms.

Table 27: Summary of mixed-effects model for health state utilities including baseline utility, age and health state (BMC)

Coefficient	Parameter value	SE	p-value
Intercept	0.350	0.049	<0.001
Baseline utility	0.657	0.025	<0.001
Age	-0.001	0.001	0.069
Health state (BMC): after	-0.064	0.014	<0.001
Model fit diagnostics			
AIC	-955.6		
BIC	-924.37		
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; BMC, baseline metastases censored at Day 0; SE, standard error.			

Table 28: Summary of mixed-effects model for health state utilities including baseline utility, age, treatment and health state (BMC)

Coefficient	Parameter value	SE	p-value
Intercept	0.347	0.049	<0.001
Baseline utility	0.656	0.025	<0.001
Age	-0.001	0.001	0.065
Treatment: darolutamide	0.007	0.010	0.494
Health state (BMC): after	-0.062	0.014	<0.001
Model fit diagnostics			
AIC	-954.07		
BIC	-917.64		
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; BMC, baseline metastases censored at Day 0; SE, standard error.			

Similar analyses were conducted using the BME metastatic progression definition. The mixed-effects model results are summarized in Appendix K.

Mapping

Mapping was not used within this economic evaluation.

Health-related quality of life studies

A systemic literature review (SLR) was performed to identify all published HRQL studies in adults with nmHRPC/nmCRPC. Full details of the systematic review for published cost-effectiveness studies are reported in Appendix H. An overview of the identified studies is presented in Table 29.

In summary, 10 studies from 16 publications met the inclusion criteria and were included in this review. Out of the 10 studies, three reported nmCRPC utility values; two were HTA submissions (NICE enzalutamide TA580 (2) and the Canadian Agency for Drugs and Technologies in Health enzalutamide (53)) and one was an

elicitation study (74). Overall, the nmCRPC and mCRPC utilities used in the cost-effectiveness model aligned with the published utilities in those studies.

Table 29: Results from health-related quality of life studies

Study name (country)	Type of study	Cohort size (response rates)	Health states	Method of elicitation and valuation	Utility data
CADTH [enzalutamide], 2019 (Canada) (53)	HTA	• NR • High-risk nmCRPC in adults	Three health states: • nmCRPC • Progressed mCRPC – PD1 – PD2 – PD3 • Death	Elicitation: NR Valuation: NR	**Manufacturer's submission** • End-of-life disutility: 0.006 **EGP** • End-of-life disutility: 0.004
Fizazi et al. 2019 (1) ARAMIS NCT02200614 (multicentre, international) (1, 75)	RCT	• N = 1,509 • Patients with nmCRPC	NR	Elicitation: EQ-5D-3L Valuation: VAS (Note: VAS and index scores both provided, tariff used for EQ-5D-3L not stated)	**EQ-5D-3L index score** LSM time-adjusted AUC (95% CI) • Darolutamide: 0.8 (0.8, 0.8) • Placebo: 0.8 (0.8, 0.8) Difference: 0.01 (−0.00, 0.02) **EQ-5D-3L VAS** LSM time-adjusted AUC (95% CI) • Darolutamide: 73.3 (72.1, 74.4) • Placebo: 72.7 (71.5, 73.9) Difference: 0.6 (−0.3, 1.5)

Study name (country)	Type of study	Cohort size (response rates)	Health states	Method of elicitation and valuation	Utility data
NICE [enzalutamide], 2019 (UK) (2)	HTA	• NR • High-risk nmCRPC in UK practice	Three health states: • nmCRPC • mCRPC – PD1 – PD2 – PD3 • Death	Elicitation: EQ-5D-5L Valuation: TTO (UK tariff)	Mean utility value ± SE (95% CI)(76) • nmCRPC: 0.852 • PD1: 0.810 • PD2: 0.798 • PD3: 0.688 ± 0.048 (0.640 to 0.735) • Pre-death: 0.590 **Disutilities of AEs** • Anaemia: -0.119 • Asthenia: -0.131 • Back pain: -0.069 • Bone pain: -0.069 • Deterioration in general physical health: -0.131 • Fall: -0.069 • Fatigue: -0.131 • Febrile neutropenia: -0.120 • Haematuria: no (dis-) utilities available • Hypertension: -0.153 • MACE: -0.153 • Neutropenia: -0.090 • Pulmonary embolism: -0.145 • Urinary retention: -0.110

Study name (country)	Type of study	Cohort size (response rates)	Health states	Method of elicitation and valuation	Utility data
					Disutilities of SREs • Spinal cord compression: -0.237 • Pathological bone fracture: -0.201 • Radiation to the bone: -0.056 • Surgery to the bone: -0.056 **Average disutility due to AE while on treatment** • Enzalutamide in nmCRPC: -0.01017 • Enzalutamide treatment in PD1: -0.00725 • ADT: -0.00508 • BSC: 0 • Docetaxel: -0.00615 **Average disutility due to SRE while on treatment** • Enzalutamide: -0.00944 • ADT: -0.00856 • BSC: -0.00856 • Docetaxel: -0.00944

Study name (country)	Type of study	Cohort size (response rates)	Health states	Method of elicitation and valuation	Utility data
Tombal et al., 2018 (77) PROSPER Trial (multicentre, international)(77)	RCT	• High risk as patient population was sourced from PROSPER trial • 146	NR	EQ-5D VAS	**Mean (SD) EQ-5D VAS score** • Enzalutamide – Baseline: 76.2 (16.92) – Week 177: 74.5 (19.31) • Placebo – Baseline: 77.5 (15.97) – Week 177: 69.0
Dawson 2018 (US) (74)	Population-based survey	• Risk not reported • 96 patients completed the TTO choice tasks	Three health states: • nmCRPC • mCRPC before chemotherapy • mCRPC either on or after chemotherapy	Vignette-based, online TTO, web-based survey	**Mean (SD)** • nmCRPC: 0.80 (0.36) • mCRPC before chemotherapy: 0.74 (0.43) • mCRPC either on or after chemotherapy: 0.64 (0.47)
US ICER 2018 (US) (51)	HTA	High risk as patient population was sourced from PROSPER and SPARTAN trial	Four health states: • MFS • Asymptomatic progression • Symptomatic progression • Death	Elicitation: EQ-5D-5L Valuation: NR	Utility value (95% CI) • MFS: 0.900 (0.720–0.990) • Metastasis/progressed disease: asymptomatic: 0.830 (0.795–0.865) • Metastasis/progressed disease: symptomatic: 0.692 (0.588–0.796) • Fracture due to cancer treatment, first year: 0.830 (0.664–0.990) • Fracture due to cancer treatment post first year: 0.870 (0.690–0.990)

Study name (country)	Type of study	Cohort size (response rates)	Health states	Method of elicitation and valuation	Utility data
Smith 2018 (SPARTAN Trial)* (multicentre, international) (31)	RCT	• Patients with nmCRPC with a high risk of developing metastases, defined as a PSA doubling time of 10 months or less • Apalutamide, N=806 • Placebo, N=401 Compliance rate: ≥ 92%, range 92-100%.	NR	EQ-5D VAS	**Change from baseline EQ-5D VAS score** Mean (SE) • Apalutamide: 1.44 (0.87) • Placebo: 0.26 (1.75)
Barocas et al., 2014 (US) (78)	Economic modelling study	Patients diagnosed with localization following biochemical	Health states: • Local treatment • Local continuing • Terminal prostate • Metastatic treatment	NR; disutilities sources from previously published literature	**Quality of life decrements:** • Local spread prostate cancer: 0.16 • Metastatic spread prostate cancer: 0.33 • Radiation treatment for prostate cancer: 0.27 • Bowel problems from treatment: 0.29

Study name (country)	Type of study	Cohort size (response rates)	Health states	Method of elicitation and valuation	Utility data
		prostate cancer recurrence	• Metastatic continuing • Death		• Impotence from treatment: 0.11 • Incontinence from treatment: 0.17 • Terminal prostate cancer: 0.75 • Terminal – all cause mortality (ages 65–84): 0.54 • Terminal – all cause mortality (ages 85+): 0.65 • Death: 1
Hechmati 2012 (France, Germany, Italy, Spain, UK) (79)	Population -based survey	High-risk mCRPC: 146 mCRPC: 680	NR	EQ-5D	**Mean (SD) EQ-5D score** • CRPC patients at a high risk of developing bone metastases (n=36): 0.77 (0.22) • CRPC patients with bone metastases (n=165): 0.59 (0.30); p=0.0001

Study name (country)	Type of study	Cohort size (response rates)	Health states	Method of elicitation and valuation	Utility data
Zubek et al., 2009 (80)	Economic modelling study	Patients with locally advanced prostate cancer with biochemical (prostate specific antigen) recurrence of after prostatectomy, N=342	The following health states were used: • Alive • Status post (S/P) local recurrence • Metastatic disease • Metastatic disease hormone refractory • Dead	Elicitation: EQ-5D Valuation: NR	• Surgery: 0.95 • Local radiation: 0.909

Key: ADT, androgen deprivation therapy; AE, adverse event; AUC, area under the curve; BSC, best supportive care; CADTH, Canadian Agency for Drugs and Technologies in Health; CI, confidence interval; EGP, Economic Guidance Panel; EQ-5D-3L, 3-level EQ-5D; HTA, health technology assessment; LSM, least-squares mean; MACE, major cardiovascular adverse event; mCRPC, metastatic castration-resistant prostate cancer; MFS, metastasis-free survival; NICE, National Institute for Health and Care Excellence; nmCRPC, non-metastatic castration-resistant prostate cancer; NR, not reported; PD progressive disease; PSA, prostate specific antigen; RCT, randomized controlled trial; SD, standard deviation; SE, standard error; SRE, skeletal-related event; TTO, time trade-off; US ICER, Institute for Clinical and Economic Review; VAS, visual analogue scale.

Note: mCRPC was further split into first-line PD1, second-line PD2, and third-line PD3.

Adverse events

In the model, any grade AEs that occurred in more ≥5% of patients and that had a grade 3/4 frequency in either group for the darolutamide or ADT arms in the ARAMIS trial were included. In addition to the negative impact on patients' QoL and increase in costs caused by AEs, SSEs are also associated with a substantial increase in healthcare resource use and reduction of the QoL among patients experiencing bone metastases. SSE rates for both arms were sourced from the ARAMIS trial, but without restrictions of grade or cut-off thresholds. The AE and SSE rates are presented in Table 30.

Consistent with the assumption in TA580, it is assumed that the majority of the AEs are resolved within 10.5 days (2, 58). Given that the EQ-5D-3L questionnaires were completed at 16 weeks, it is unlikely that the impact of AEs and SSEs on HRQL was captured in the trial-based analysis. Therefore, individual disutilities are modelled to capture the HRQL impact of AEs and SSEs. The durations of AEs and SSEs used for estimating the impact on QoL were taken from previous prostate cancer NICE appraisals TA580 (2) and TA377 (58) (enzalutamide for mHRPC). Table 31 summarizes the AE and SSE disutilities and durations used in the model, Table 32 summarizes the resulting one-off quality-adjusted life year (QALY) decrements applied at the first cycle. The model only considers AEs and SSEs associated with the initial nmCRPC treatments. Given the lack of publicly available data regarding AEs and SSE frequency for subsequent therapies in the mCRPC state, as a simplifying assumption AEs and SSEs associated with subsequent mCRPC treatments are not considered in the model because this is believed to have minimal impact on the incremental cost-effectiveness ratio (ICER).

Table 30: AEs and SSE rates (per patient per lifetime) (1)

Event rates	Darolutamide + ADT (ARAMIS N=954)	ADT (ARAMIS N=554)
AEs		
Anaemia	0.008	0.004
Arthralgia	0.003	0.004
Back pain	0.004	0.002

Company evidence submission template for darolutamide for treating non-metastatic hormone-relapsed prostate cancer [ID1443]

Event rates	Darolutamide + ADT (ARAMIS N=954)	ADT (ARAMIS N=554)
Diarrhoea	-	0.002
Fatigue	0.004	0.009
Hypertension	0.031	0.022
Nausea	0.002	-
Pain in an extremity	-	0.002
Urinary retention	0.016	0.020
Urinary tract infection	0.006	0.005
SSEs		
Spinal cord compression	0.002	0.002
Pathological bone fracture	-	0.002
Key: ADT, androgen deprivation therapy; AE, adverse event; SSE, symptomatic skeletal event.		

Table 31: AEs and SSEs duration and disutilities

	Disutility	Source	Duration (days) – source: NICE TA580 (2)/TA377 (58)
AEs			
Anaemia	-0.119	Swinburn 2010 (81). Same source used in NICE TA580 (2) and TA377 (58)	10.50
Arthralgia	-0.070	Doyle 2008 (82). Same source used in NICE TA377 (58)	10.50
Back pain	-0.069	Doyle 2008 (82). Same source used in NICE TA580 (2) and TA377 (58).	10.50
Diarrhoea	-0.103	Doyle 2008 (82).	10.50
Fatigue	-0.131	Lloyd 2006, Nafees 2008, Swinburn 2010. Same source used in NICE TA580 (2) and TA377(58)	91.25
Hypertension	-0.153	Swinburn 2010 (81). Same source used in NICE TA580 (2) and TA377(58)	10.50
Nausea	-0.048	Nafees 2008 (83)	10.50

	Disutility	Source	Duration (days) – source: NICE TA580 (2)/TA377 (58)
Pain in an extremity	-0.069	Assumed same as back pain	10.50
Urinary retention	-0.110	Armstrong 2009 (84)	10.50
Urinary tract infection	-0.070	Armstrong 2009 (84)	10.50
SSEs			
Spinal cord compression	-0.237	NICE TA580 (2)/TA377 (58), based on the PREVAIL trial (85)	30.42
Pathological bone fracture	-0.201		30.42
Key: AE, adverse event; NICE, National Institute for Health and Care Excellence; SSE, symptomatic skeletal event.			

Table 32: Weighted one-off QALY decrements applied in the model

Treatment arm	QALY decrement
AEs	
Darolutamide	-0.00038
ADT	-0.00050
SSEs	
Darolutamide	-0.00004
ADT	-0.00007
Key: ADT, androgen deprivation therapy; AE, adverse event; QALY, quality-adjusted life year; SSE, symptomatic skeletal event.	

Health-related quality of life data used in the economic model

Given the lack of significant difference observed between treatment arms in the utility analysis (Table 28), for the model base case, the pooled BMC mixed-effects model (without the treatment arm covariate) was used to estimate the metastatic progression-free health state utility. This approach, which is consistent with the base case choice of BMC for the modelling of efficacy, conservatively assumed that all treatment arms will have the same utility value. As individual AE and SSE disutilities

are included in the model, the treatment arm covariate was excluded in the model base case to avoid double counting the impact of AEs and SSE disutilities; this is potentially a conservative assumption as treatment with darolutamide was associated with an increase in utility (though not significant) in both the BMC and BME models.

As the EQ-5D-3L collection in ARAMIS was limited to the initial stages of the trial, it was not possible to use trial-based robust post-progression utility values due to the small number of observations for patients who had confirmed metastases. As suggested by clinical experts in the validation meeting, an average utility for the mCRPC state would be able to capture the QALYs associated with the subsequent treatments at each line of therapy (first-, second-, third-line and best supportive care [BSC]) in the mCRPC state and is expected to range approximately between 0.6–0.7 (3). As such, a weighted average utility in the mCRPC state was estimated based on the average time spent in each of the mCRPC states from previous mCRPC appraisals. The proportions of time spent in each line of therapy in the metastatic disease state (mCRPC 1, mCRPC 2, mCRPC 3 and BSC) were sourced from TA377 (58), as it was deemed the most relevant publicly available information given that disaggregated life years results were redacted in TA580 (2, 76). This approach assumed that all treatment arms have the same utility value. The estimated weighted utility average is 0.7, in line with the clinical experts' estimation (3). In addition, to test model sensitivity to health state utility values, alternative mCRPC utility values reported in NICE TA580 (76) and TA412 (60) were used in scenario analyses.

Table 33: mCRPC weighted average utility

	mCRPC 1	mCRPC 2	mCRPC 3	mCRPC BSC (palliative care)
Mean LYs* (58)	0.601	0.586	0.438	0.988
Utility (64, 76)**	0.81	0.80	0.688	0.59
Average weighted utility	0.704			
Utility source (64, 76)	EQ-5D data in PROSPER		Originally sourced from AFFIRM (TA316)	Originally sourced from the PREVAIL

Key: BSC, best supportive care; LYs, life years; mCRPC, metastatic castration resistant prostate cancer; TA, technology appraisal; BSC, best supportive care.

*sourced from TA377 Table B83 in the company submission.

**sourced from TA580 and SMC2195.

A summary of the health state utility values used in the model base case is presented in Table 34.

Table 34: Summary of utility values used in the cost-effectiveness analysis

State	Utility value: mean (standard error)	Reference in submission (section and page number)	Justification
nmCRPC – all arms	0.813 (0.081)	(see section B.3.4 page 131)	ARAMIS is the main source of utility weight values for the nmCRPC health state
mCRPC – all arms	0.704 (0.070)	(section B.3.4 page 131)	Small number of metastatic observations from ARAMIS, as such weighted average utility for the mCRPC state was used as suggested by

State	Utility value: mean (standard error)	Reference in submission (section and page number)	Justification
			clinical experts' in the validation meeting
AEs			
Anaemia	-0.119	(see section B.3.4 page 129)	Literature values were used given that the impact of individual AEs could not be measured in the ARAMIS trial due to frequency of the collected HRQL data
Arthralgia	-0.070		
Back pain	-0.069		
Diarrhoea	-0.103		
Fatigue	-0.131		
Hypertension	-0.153		
Nausea	-0.048		
Pain in an extremity	-0.069		
Urinary retention	-0.110		
Urinary tract infection	-0.070		
SSEs			
Spinal cord compression	-0.237 (0.079)	(see section B.3.4 page 129)	Disutilities reported for different types of SSEs in patients with bone metastases
Pathological bone fracture	-0.201 (0.080)		
Key: AE, adverse event; HRQL, health-related quality of life; nmCRPC, non-metastatic castration-resistant prostate cancer; SSE, symptomatic skeletal event.			

B.3.5. Cost and healthcare resource use identification, measurement and valuation

Costs used within the model reflect the UK NHS and PSS perspective. As such, only direct medical costs were considered, consisting 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

Resource use and unit costs for the economic model were obtained from the National Schedule of Reference Costs, Personal Social Services Research Unit (PSSRU), and previous technology appraisals in prostate cancer, described in more detail below. All model costs were inflated to 2018/2019, where appropriate, using inflation indices from the 2019 PSSRU (68).

An SLR was also conducted to source any appropriate costs or resource use data for adults with nmCRPC, full details of which are in Appendix I. Of the identified studies, only seven met the inclusion criteria and were, therefore, included in this review. Of the seven publications, only one study was relevant to the NHS England and Wales clinical settings: the NICE enzalutamide appraisal for nmCRPC. However, the SLR did not identify healthcare resource use specific for the nmCRPC state and patients in the UK. As such, in collaboration with IQVIA, Bayer conducted a healthcare resource use study to better understand the healthcare resource use utilization in the nmCRPC patient population (86). Details of this study are presented in the section below.

Intervention and comparators' costs and resource use

Generic drug costs were sourced from the electronic market information tool (eMIT), branded products were sourced from the Monthly Index of Medical Specialities. Table 35 presents the model drug costs and dosing schedule for darolutamide and ADTs. For oral therapies, it was assumed that patients will not share unused tablets, in line with clinical practice.

ToT data for darolutamide are sourced from the ARAMIS patient-level data. The methods used to estimate the ToT data are described in Section B.3.3. The cost of darolutamide per treatment cycle is applied to the proportion of patients treated with darolutamide based on this extrapolated curve. A proposed simple patient access scheme (PAS) of [redacted] is applied to the acquisition cost of darolutamide.

For the ADT arm, in line with the ARAMIS trial and based on clinical experts' opinion, a blended basket of common ADTs – including leuprorelin (40%), goserelin (30%), triptorelin (20%) and buserelin (10%) – was used to represent the ADT arm (3). Moreover, clinical experts confirmed that no background steroid treatments are currently used in the UK clinical practice (3). In line with UK clinical practice (informed by the clinical experts' opinion), the costs of the blended basket of ADT are equally applied to both arms across the entire model time horizon (3). This is also consistent with the assumption in the NICE enzalutamide appraisal for nmHRPC (2).

In addition to drug acquisition costs, the cost of administration was considered for darolutamide and the basket of ADT (Table 36). As darolutamide and buserelin are oral therapies they do not require hospital administration, but patients are assumed to incur a dispensing fee cost of £9 (68). For all subcutaneous therapies, an administration cost of £28 was applied (68). Costs associated with each treatment administration are summarized in Table 37.

The SmPC for buserelin states that an initiation therapy is administered to patients, usually in hospital, where 0.5 ml of buserelin is injected subcutaneously at eight-hour intervals for 7 days (87). Maintenance therapy then follows from the eighth day of treatment, where a single dose of nasal spray is introduced into each nostril six times a day (at home). However, as ADT costs are equally applied to all arms for the entire model time horizon, and given that clinical experts suggested that it would be given either in hospital or in the community (3), we simplified the costing approach and only considered the maintenance dose/cost for the whole ADT period.

Table 35: Drug costs for darolutamide and ADT

Drug	Unit	Unit cost (list price)	Dosing	Cost per model cycle	Source for drug costs and dosing
Darolutamide	112 x 300 mg tablets	£4,040.00	1,200 mg daily, oral	£4,040.00 (list price) [redacted]	
Basket of ADT					
Leuprorelin (Lutrate 1-month depot)*	3.75 mg	£75.24	3.75 mg monthly implant	£69.21	MIMS (88, 89)
Goserelin	3.6 mg x 3.8 mg implant	£70.00	3.6 mg intramuscular injection Q4W	£70.00	MIMS (90, 91)
Triptorelin (Decapeptyl)**	3 mg	£69.00	3 mg subcutaneous injection Q4W	£69.00	MIMS (92, 93)
Buserelin	4 x 100 microgram	£122.24	1 spray dose per day	£102.68	MIMS (94, 95)
Total ADT and background therapy costs					
First cycle	£72.75				
Thereafter	£72.75				
Key: ADT, androgen deprivation therapy; MIMS, Monthly Index of Medical Specialities; Q4W, every 4 weeks. **Notes:** *, assumed Lutrate as this is cheaper than Prostap, the cost of 1 month and 3 months is the same per mg so 1 month applied; **, assumed Decapeptyl as cheaper than Gonapeptyl.					

Table 36: Drug administration costs

Mode of administration	Drug administration cost	Reference
Oral	£9	Cost of 12 minutes of pharmacist time, Personal Social Services Research Unit 2018/2019 (68)
Intravenous infusion	£259.08	Deliver more complex parenteral chemotherapy at first attendance, outpatient (SB13Z), National Health Service reference costs 2018/2019 (65)
Subcutaneous injection	£28.00	Cost per working hour for band 4 hospital-based nurses, Personal Social Services Research Unit 2018/2019 (68)

Table 37: Administration costs for darolutamide and comparators

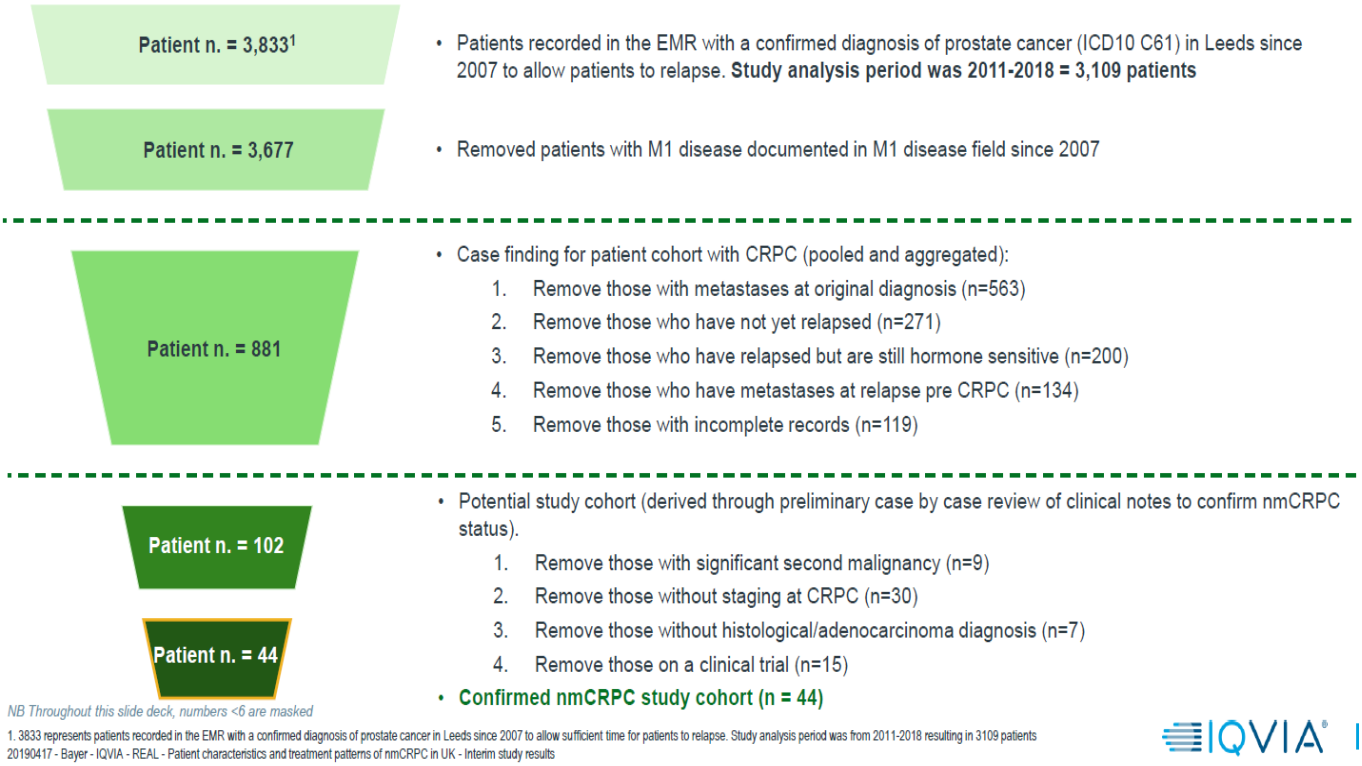
Treatments	Cost per administration	Cost per model cycle	Source
Darolutamide		£9	Cost of 12 minutes of pharmacist time, Personal Social Services Research Unit 2018/19 (68)
Basket of ADT			
Leuprorelin (Lutrate 1-month depot)	£28.00	£25.76	Subcutaneous injection; cost per working hour for Band 4 hospital based nurses, Personal Social Services Research Unit 2018/2019, page 151 (68)
Goserelin	£28.00	£28.00	Assumed implant is same cost as subcutaneous injection

Treatments	Cost per administration	Cost per model cycle	Source
Triptorelin (Decapeptyl)	£28.00	£28.00	Assumed intramuscular injection same as subcutaneous injection cost
Buserelin		£9	Assumed nasal spray is same cost as oral
Total weighted administration cost for ADT per model cycle			**£25.20**
Key: ADT, androgen deprivation therapy.			

Health state unit costs and resource use

Based on the cost and healthcare resource use SLR, no healthcare resource use frequencies were reported for patients in the nmCRPC state in the UK. As such a study, funded by Bayer and led by IQVIA, was conducted to understand healthcare resource use and costs of nmCRPC patients prior to and following occurrence of metastasis. This was a retrospective cohort study using both structured data from hospital electronic medical records and unstructured information derived from clinical notes through a process of data enhancement by a clinical specialist. The study setting was REAL-Oncology, an IQVIA collaboration accessing longitudinal data from a large NHS trust. The trust serves a metropolitan catchment area of over 750,000 for secondary care and more than 5 million patients in tertiary care. The study population consisted of patients considered to have nmCRPC based on evidence of castration resistance (luteinizing hormone-releasing hormone treatment or surgical castration) and rising PSA (one rise) in the absence of metastatic disease. A schematic of the cohort of patients in this study is presented in Figure 25. The study time period was 1 January 2011 to 31 January 2019 (86).

Figure 25: A schematic figure displaying the identification of the cohort of patients used in the study (86)



Key: CRPC, castration-resistant prostate cancer; EMR, electronic medical record; M1, metastatic; nmCRPC, non-metastatic castration-resistant prostate cancer.

The frequencies of resource utilisation from this study were used in the model base case. In line with other prostate cancer NICE appraisals investigating ADTs (TA580 and TA377) (2, 58) and based on UK clinical experts' opinion, it was assumed that all treatment arms would have the same healthcare resource use (see Table 38). Unit costs were sourced from the latest NHS reference costs (2018–19) and the PSSRU 2019 (68) (Table 38). As an alternative scenario, healthcare resource use frequencies from part of the TA580 appraisal were used. In this scenario, as well as assuming equal healthcare resource use between arms, in TA580 (2) it was assumed that the nmCRPC and mCRPC health states would also have the same healthcare resource use (£126.08 per 28-day cycle).

All patients were assumed to incur a palliative care cost before death. This included costs related to hospital care in the 90 days before dying, based on Georghiou and Bardsley (2014) (96), including a district nurse, nursing and residential care, hospital care and Marie Curie nursing costs. A one-off terminal care cost of £7,761, after adjustment for inflation, was applied to patients upon entry to the death health state (see Table 39).

Table 38: Summary of health states and associated resource use costs included in the economic model

Healthcare resource use	nmCRPC state frequency (per 28-days) – all arms	mCRPC state frequency (per 28-days) – all arms	Unit costs	Sources
Outpatient visit – consultant			£109.00	Cost per hour for hospital doctors (consultant medical), Section 14 in PRSSU 2019 page 158 (consultant medical) (68)
Outpatient visit – nurse			£38.00	Cost per hour for band 5 hospital based nurses, Section 13 in PRSSU 2019 page 155 (68)
Community nurse visit			£37.00	Cost per hour for band 5 community based nurses, Section 10.1 in PRSSU 2019 page 125 (68)
A&E visit			£168.33	NHS reference cost 2018/2019: Total Outpatient Attendances: 180 Accident and emergency (Total) (65)
CT scan			£115.56	NHS reference cost 2018/2019: IMAGOP RD26Z, CT of three areas with contrast (65)
Bone scan			£271.30	NHS reference cost 2018/19: Weighted average of IMAGOP RN15A and RN16A, nuclear bone scans, 19 years and over (65)
Full blood count			£2.79	NHS reference cost 2018/2019: DAPS, haematology: DAPS05
Liver function test			£1.10	NHS reference cost 2018/2019: DAPS, clinical biochemistry: DAPS04 (65)
Kidney function test			£1.10	NHS reference cost 2018/2019: DAPS, clinical biochemistry: DAPS04 (65)

Healthcare resource use	nmCRPC state frequency (per 28-days) – all arms	mCRPC state frequency (per 28-days) – all arms	Unit costs	Sources
PSA count	[redacted]	[redacted]	£1.10	NHS reference cost 2018/2019: DAPS, clinical biochemistry: DAPS04 (65)
Testosterone test	[redacted]	[redacted]	£1.10	NHS reference cost 2018/2019: DAPS, clinical biochemistry: DAPS04 (65)
Metabolic panel/ biochemistry	[redacted]	[redacted]	£1.10	NHS reference cost 2018/2019: DAPS, clinical biochemistry: DAPS04 (65)
Blood and electrolytes	[redacted]	[redacted]	£1.10	NHS reference cost 2018/2019: DAPS, clinical biochemistry: DAPS04 (65)
Bone profile	[redacted]	[redacted]	£131.01	NHS reference cost 2018/2019: Total Outpatient Attendances: 822 Chemical pathology (65)
X-ray	[redacted]	[redacted]	£30.59	NHS reference cost 2018/2019: DADS: DAPF Direct Access Plain Film (65)
Inpatient hospitalizations-overnight admission nmCRPC	[redacted]	[redacted]	£3,441.93	This is estimated by the sum of : 1. Inpatient hospitalization – overnight admission and, 2. Inpatient hospitalization – overnight admission excess bed; where the average number of hospitals stays days is estimated by the difference in the estimated average number of days from the reported NHS stay for EL: LB06N-LB606S (2017/2018 NHS reference costs*) and the estimated number of hospitalization days estimated from the IQVIA study for the nmCRPC period (86)

Healthcare resource use	nmCRPC state frequency (per 28-days) – all arms	mCRPC state frequency (per 28-days) – all arms	Unit costs	Sources
Inpatient hospitalizations-day case	[redacted]	[redacted]	£751.90	NHS reference cost 2018/2019: Total index day case (65)
Inpatient hospitalizations-overnight admission mCRPC	[redacted]	[redacted]	£4,888.43	This is estimated by the sum of : 1. Inpatient hospitalization – overnight admission and, 2. Inpatient hospitalization – overnight admission excess bed; where the average number of hospitals stays days is estimated by the difference in the estimated average number of days from the reported NHS stay for EL: LB06N-LB606S (2017/2018 NHS reference costs*) and the estimated number of hospitalization days estimated from the IQVIA study for the mCRPC period (86)
Inpatient hospitalizations-overnight admission	N/A	N/A	£1,707.93	NHS reference cost 2018/2019: Weighted average EL: LB06N-LB606S Kidney, Urinary Tract or Prostate Neoplasms, without Interventions, with CC Score 0-1 to13+ (65)
Inpatient hospitalizations-overnight admission excess bed	N/A	N/A	£399.00	NHS reference cost 2017/2018: Weighted average EL_XS: LB06N-LB606S Kidney, Urinary Tract or Prostate Neoplasms, without Interventions, with CC Score 0-1 to13+ (65)
Total costs per model cycle	**£190.71**	**£459.85**		

Healthcare resource use	nmCRPC state frequency (per 28-days) – all arms	mCRPC state frequency (per 28-days) – all arms	Unit costs	Sources
Key: A&E, accident and emergency; CT, computed tomography; mCRPC, metastatic castration-resistant prostate cancer; NHS, National Health Service; nmCRPC, non-metastatic castration-resistant prostate cancer; PSA, prostate specific antigen; PSSRU, Personal Social Services Research Unit. **Note:** The NHS reference costs 2017/2018 was used as the 2018/2019 version does not report the average Length of Stay in days for elective inpatient EL costing code				

Table 39: Palliative care costs

Cost	Unit cost	Reference	2018/19 uplifted cost (PSSRU 2019) (68)
District nurse	£278	Georghiou and Bardsley (2014) (96)	£312
Nursing and residential care	£1,000		£1,157
Hospital care – inpatient	£550		£618
Hospital care – final 3 months of life	£4,500		£5,055
Marie Curie nursing service	£550		£618
Total			**£7,761**
Key: PSSRU, Personal Social Services Research Unit.			

Adverse events unit costs and resource use

AE and SSE related costs were applied as one-off costs in the model. Unit costs were sourced from the latest NHS reference costs (2018/2019) (65) and are presented in Table 40. The one-off AE and SSE costs applied to each treatment arm are summarized in Table 41.

Table 40: AEs and SSEs costs used in the model

	Unit cost	Source
AEs		
Anaemia	£2,337.50	NHS reference costs 2018/2019; NEL: weighted average of SA04G, SA04H, SA04J, SA04K, SA04L (65). Same source used in NICE TA580 (2).
Arthralgia	£377.51	Assume same as back pain
Back pain	£377.51	NHS reference costs 2018/2019; NES: weighted average of HC32G, HC32H, HC32J, HC32K (65)
Diarrhoea	£477.21	Assume same as nausea
Fatigue	£348.49	NHS reference cost 2018/2019, NES: weighted average: AA31C, AA31D, AA31E, DZ38Z (65). Same source used in NICE TA391 (61)
Hypertension	£338.57	NHS reference cost 2018/2019, NES EB04Z (65). Same source used in NICE TA580 (2)
Nausea	£477.21	NICE TA412 (60) company submission (Table 12), based on NHS reference costs 2014/2015 weighted average: FZ91A, FZ91B, FZ91C, FZ91D, FZ91E, FZ91F, FZ91G, FZ91H, FZ91J, FZ91K, FZ91L, FZ91M. Inflated to 2018/2019 cost
Pain in an extremity	£377.51	Assume same as back pain
Urinary retention	£2,156.91	NHS reference costs 2018/2019; NEL: weighted average of LB16D, LB16E, LB16F, LB16G, LB16H, LB16J, LB16K (65). Same source used in NICE TA580 (2)

	Unit cost	Source
Urinary tract infection	£2,652.37	NHS reference costs 2018/2019; NEL: weighted average of LA04H, LA04J, LA04K, LA04L, LA04M, LA04N, LA04P, LA04Q, LA04R, LA04S (65)
SSE		
Spinal cord compression	£6,184.46	NHS reference costs 2018/2019; NEL: weighted average of HC28H, HC28J, HC28K, HC28L, HC28M (65). Same source used in NICE TA580 (2)
Pathological bone fracture	£3,752.41	NHS reference costs 2018/2019; NEL: weighted average of HD39D, HD39E, HD39F, HD39G, (65) HD39H. Same source used in NICE TA580 (2)
Key: AE, adverse event; NEL, non-elective long stay; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; SSE, symptomatic skeletal event.		

Table 41: AE and SSE one-off costs used in the model

Treatment arm	AE one-off cost	SSE one-off cost
Darolutamide + ADT	£86.08	£12.97
ADT	£79.69	£17.94
Key: ADT, androgen deprivation therapy; AE, adverse event; SSE, symptomatic skeletal event.		

Miscellaneous unit costs and resource use

Subsequent treatment costs

Given ARAMIS' international recruitment, the relatively short follow-up compared with the expected long-term nature of mCRPC, and the double-blind nature of the trial, the subsequent treatments observed in the ARAMIS trial may not accurately represent the subsequent treatments used to manage mCRPC in the UK, especially in later lines. As such, in the model base case the subsequent treatment distributions

were sourced from the clinical validation advisory board, where during a workshop, 10 leading clinical experts from across the UK (nine oncologists and one urologist) were divided in two groups and reached consensus on the subsequent treatment distribution that is expected in UK clinical practice. In both groups it was agreed that enzalutamide would not be given at any line of therapy following progression on the darolutamide + ADT arm and that bicalutamide is not used in the mCRPC state in either arms. The responses of the two groups in the workshop were very closely aligned and the average estimates from both groups was used in the model base case. The average number of patients experiencing a first, secondary and tertiary progression was estimated from the model based on the proportion of patients alive at time of progression for each arm. The time of experiencing the first progression was approximated by the undiscounted mean MFS LYs for each arm. As for the time of the secondary and tertiary progressions, these were estimated based on a weighted average duration that a patient would spend in the previous lines using the distribution at each line and the mean treatment durations sourced from published literatures (58, 59, 97). Given that >80% of patients are estimated to be on BSC at fourth-line, and given that they do not incur any medicines-related costs, subsequent treatment costs only for the first three lines of therapies in the mCRPC were considered in the model. As the model has one mCRPC health state, subsequent treatment costs were applied as a one-off cost, representing the basket of subsequent treatments used across all mCRPC treatment lines upon exiting the MFS health state.

Table 42: Subsequent treatment types and distributions in the UK base case – based on the average estimates from Bayer advisory board (3)

	Darolutamide + ADT arm				**ADT arm**			
Treatment	**First-line**	**Second-line**	**Third-line**	**Sum**	**First-line**	**Second-line**	**Third-line**	**Sum**
No treatment/BSC	12.9%	24.8%	52.8%	**90.6%**	3.0%	10.7%	31.8%	**45.4%**
Abiraterone	1.8%	3.5%	1.6%	**7.0%**	36.8%	3.6%	1.6%	**41.9%**

	Darolutamide + ADT arm				ADT arm			
Treatment	**First-line**	**Second-line**	**Third-line**	**Sum**	**First-line**	**Second-line**	**Third-line**	**Sum**
Enzalutamide	0.0%	0.0%	0.0%	**0.0%**	36.8%	3.6%	1.6%	**41.9%**
Docetaxel	44.4%	10.6%	0.0%	**55.0%**	8.7%	35.7%	3.2%	**47.5%**
Radium-223	14.8%	14.2%	4.9%	**33.9%**	1.3%	14.3%	12.7%	**28.3%**
Cabazitaxel	0.0%	17.7%	6.6%	**24.3%**	0.0%	3.6%	12.7%	**16.3%**
Bicalutamide	0.0%	0.0%	0.0%	**0.0%**	0.0%	0.0%	0.0%	**0.0%**
Proportion of patients experiencing progression	**74.0%**	**70.9%**	**66.0%**		**86.5%**	**71.3%**	**63.5%**	
Average time of progression (years)	**4.1**	[redacted]	[redacted]		**2.0**	[redacted]	[redacted]	
Key: ADT, androgen deprivation therapy; BSC, best supportive care.								

In addition to the model base case, two alternative scenarios were explored in the model. In the first, the average estimates from the ERG and UK Cancer Drugs Fund from TA580 (76) were used. In the second alternative scenario, the most frequently used subsequent treatment types and distributions observed in the ARAMIS trial were explored, based on first-line and on all lines of subsequent treatment. Table 44 presents the most frequently used subsequent treatments and distributions based on the ARAMIS trial. Subsequent treatments received by ≥5% of patients who had metastatic progression in the ARAMIS trial were included in the model, except those treatments that were suggested by the clinical experts in the model base case; in which case, those were included without any cut-off. Moreover, to account for subsequent treatments not frequently used in the trial and not reflective of the NHS clinical settings, those treatment proportions were added to the total share of the no treatment/BSC treatment option.

The durations of subsequent treatments were sourced from the literature. Abiraterone, enzalutamide and cabazitaxel (Jevtana®) were assumed to have mean durations of 13.8, 17.71 and 8.8 months, respectively, based on reported median ToT from respective NICE appraisals in prostate cancer(58, 59), as well as reported median time to progression in TA391 for cabazitaxel. For radium-223, the mean duration of treatment is [redacted] (97). For docetaxel and bicalutamide subsequent treatment, the mean durations estimated from ARAMIS trial data were 75.7 and 135 days, respectively, based on patients who had documented start and end dates for these treatments.

Drug acquisition and administration costs associated with subsequent treatments for mCRPC are provided in Table 45 and Table 46, where list price was used for all drugs where appropriate except for radium-223 where the PAS of [redacted] was provided by Bayer. However, for drugs that are known to be offered under a simple discount scheme to the NHS, such as enzalutamide, abiraterone and cabazitaxel, a threshold analysis was conducted and presented in Appendix L to further test the ICER for a range of possible discounts for all treatments independently.

A weighted one-off cost for subsequent treatments was estimated for each treatment arm based on the distribution of patients receiving each type of subsequent treatment (see Table 43), resulting in one-off weighted subsequent treatment drug costs of [redacted] and [redacted], and drug administration costs of [redacted] and [redacted] for the darolutamide + ADT and ADT arms, respectively. These one-off costs were applied to the proportion of patients moving into the mCRPC health state in each model cycle.

Given that subsequent treatment costs are applied as a one-off cost upon metastatic progression, and given that they are administered only for a given number of cycles based on the mean treatment duration, discounting was applied while accounting for the greater discount that applies to the later doses of subsequent treatments; that is, the discount rate for each patient entering the metastatic state is estimated by averaging the discount rates between the time a patient enters the metastatic disease state and the estimated total average treatment duration over the three lines

of therapy. The weighted total average treatment duration was estimated by taking the weighted sum of the reported mean treatment duration using the distribution of treatments at each line of therapy, resulting in [redacted] weeks and [redacted] weeks in the darolutamide + ADT and ADT arms in the base case, respectively.

The subsequent treatments and distributions in the model only affect the costs and were assumed to have no impact on OS. This is a limitation of the model as the modelled efficacy is linked to the subsequent treatments received in the clinical trials. However, on balance it was deemed more appropriate to represent clinically relevant subsequent treatments, distributions and costs based on local settings for the model base case. However, where the modelled subsequent treatments of the ADT arm may counter any OS benefit from first-line darolutamide, a scenario considering equal efficacy from 8.7 years for both arms was shown to have limited impact on the ICER.

Important patient characteristics such as age, height and weight were sourced from the ARAMIS trial (1). As such, body surface area was calculated using the reported height and weight, using the DuBois Formula to inform drug costs (98). Drug wastage has been assumed in the base case, as this is more likely to reflect the use of therapies in clinical practice. Given that the weight and body surface area based drugs used in the economic model are part of the basket of subsequent therapies (docetaxel and cabazitaxel) given to a small number of number of patients post progression, and because their cost is relatively cheap, a simplistic approach was adopted to account for wastage whereby the required number of vials is rounded up to the nearest integer.

Table 43: Subsequent treatment types and distributions in the UK base case – based on NICE TA580 ERG and CDF average estimates (76)

	Darolutamide + ADT arm				ADT arm			
Treatment	**First-line**	**Second-line**	**Third-line**	**Sum**	**First-line**	**Second-line**	**Third-line**	**Sum**
No treatment/BSC	14.8%	36.6%	48.9%	**100.3%**	0.0%	34.0%	32.5%	**66.5%**

	Darolutamide + ADT arm				ADT arm			
Treatment	**First-line**	**Second-line**	**Third-line**	**Sum**	**First-line**	**Second-line**	**Third-line**	**Sum**
Abiraterone	0.0%	0.0%	0.0%	**0.0%**	21.6%	0.0%	0.0%	**21.6%**
Enzalutamide	37.0%	0.0%	0.0%	**37.0%**	64.9%	0.0%	0.0%	**64.9%**
Docetaxel	22.2%	13.3%	0.0%	**35.5%**	0.0%	30.6%	0.0%	**30.6%**
Radium-223	0.0%	16.6%	3.1%	**19.7%**	0.0%	3.4%	20.7%	**24.1%**
Cabazitaxel	0.0%	0.0%	9.2%	**9.2%**	0.0%	0.0%	5.9%	**5.9%**
Proportion of patients experiencing progression	**74.0%**	**70.9%**	**66.0%**		**86.5%**	**71.3%**	**63.5%**	
Average time of progression (years)	**4.1**	[redacted]	[redacted]		**2.0**	[redacted]	[redacted]	
Key: ADT, androgen deprivation therapy; BSC, best supportive care; CDF, Cancer Drug Fund; ERG, evidence review group.								

Table 44: Most frequently used subsequent treatment types and distributions observed in the ARAMIS trial – scenario analysis

Treatment	Darolutamide +ADT (all lines)	ADT arm (all lines)	Darolutamide + ADT (first subsequent treatment)	ADT arm (first subsequent treatment)
No treatment/BSC (others)	29.0%	18.5%	22.0%	11.5%
Abiraterone	22.0%	24.6%	13.0%	17.7%
Enzalutamide	28.0%	23.1%	18.0%	14.6%
Docetaxel	59.0%	56.2%	49.0%	50.8%
Cabazitaxel	3.0%	3.1%	0.0%	0.0%

Bicalutamide	6.0%	6.2%	5.0%	6.2%
Key: ADT, androgen deprivation therapy; BSC, best supportive care.				

Table 45: Subsequent treatment drug costs and dosing

Drug	Unit	Unit cost (list price)	Dosing	Cost per model cycle	Source
Docetaxel	1 ml x 20.0 mg/ml	£5.13	75 mg/m^2 Q3W, IV (99)	£22.40	eMIT, June 2018 (67)
	4 ml x 20.0 mg/ml	£13.74			eMIT, June 2018 (67)
	8 ml x 20.0 mg/ml	£16.80			eMIT, June 2018 (67)
Abiraterone	52 x 500.0 mg tablets	£2,735.00	1,000 mg daily, oral (100)	£2,735.00	MIMS, accessed 21 January 2020 (66)
Enzalutamide	112 x 40.0 mg tablets	£2,734.67	160mg daily (101)	£2,734.67	MIMS, accessed 21 January 2020 (102)
Radium-223	6 mlx 1000.0 mg/ml (KBq)	List price £4,040.00 Price with a [redacted] PAS [redacted]	55 kBq/kg Q4W, IV (103)	[redacted]	Bayer
Cabazitaxel	1.5 ml x 60.0 mg	£3,696.00	25 mg/m^2 Q3W, IV (104)	£4,928.00	MIMS (66)
Bicalutamide	28 x 50.0 mg tablets	£2.87	50 mg daily, oral (105)	£2.87	eMIT, June 2018 (67)
Key: eMIT, electronic market information tool; IV, intravenous infusion; MIMS, Monthly Index of Medical Specialities; PAS, patient access scheme; Q3W, every 3 weeks; Q4W, every 4 weeks.					

Table 46: Subsequent treatment costs applied in the model

Treatment	Average one-off drug costs	Average one off-drug admin costs
Abiraterone	£41,028.66	£135.01
Enzalutamide	£52,647.10	£173.27
Docetaxel	£60.56	£1,032.34
Radium-223	[redacted]	[redacted]
Cabazitaxel	£47,141.60	£3,652.73
Bicalutamide	£54.31	£170.33
Key: ADT, androgen deprivation therapy.		

B.3.6. Summary of base case analysis inputs and assumptions

Summary of base case analysis inputs

Table 47: Summary of base case analysis inputs

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Model controls			
Time horizon (years)	27	NA	Section B.3.2
Cycle length (days)	28	NA	
Discount rate for costs	3.5%	NA	
Efficacy discount rate	3.5%		
Patients' characteristics			
Mean age	73.62	Normal (57.15–85.01)	Section B.3.2
Mean body weight	171.18	Normal (57.15–85.01)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Mean body height	83.36	Normal (132.81–197.56)	
Mean body surface area	1.86	Normal (1.43–2.13)	
Administration costs			
Administration cost – oral	£9.00	Gamma (7.32–10.85)	Section B.3.5B.3.2
Administration cost – IV	£259	Gamma (184.51–343.45)	
Administration cost – subcutaneous injection	£28.00	Gamma (22.78–33.75)	
Drug costs			
Drug costs – darolutamide	£4,040.00	Gamma (3,287.10–4,869.37)	Section B.3.5
Drug costs – enzalutamide	£2,734.67	Gamma (2,225.04–3,296.07)	
Drug costs – leuprorelin	£75.24	Gamma (105.26–155.93)	
Drug costs – goserelin	£70.00	Gamma (211.54–313.37)	
Drug costs – triptorelin (Decapeptyl)*	£69.00	Gamma (£61.22–£90.69)	
Drug costs – buserelin	£122.24	Gamma (56.95–84.37)	
Drug costs – docetaxel 20 mg 1 ml vial	£5.13	Gamma (4.82–5.45)	
Drug costs – docetaxel 20 mg 4 ml vial	£13.74	Gamma (13.29–14.20)	
Drug costs – docetaxel 20 mg 8 ml vial	£16.80	Gamma (16.45–17.15)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Drug costs – abiraterone	£2,735.00	Gamma (2,225.30–3,296.47)	
Drug costs – radium-223	£4,040.00	Gamma (3,287.10–4,869.37	
Drug costs – cabazitaxel	£3,696.00	Gamma (3,007.21–4,454.75)	
Drug costs – bicalutamide	£2.87	Gamma (2.34–3.46)	
Subsequent treatment durations			
Subsequent treatment duration – Abiraterone	60.01	Normal (48.24–71.76)	Section B.3.5
Subsequent treatment duration – ADT	47.02	Normal (37.80–56.23)	
Subsequent treatment duration – enzalutamide	77.01	Normal (61.91–92.09)	
Subsequent treatment duration – docetaxel	10.81	Normal (8.69–12.93)	
Subsequent treatment duration – radium-223	[redacted]	[redacted]	
Subsequent treatment duration – cabazitaxel	38.26	Normal (30.76–45.7)	
Subsequent treatment duration – bicalutamide	75.70	Normal (60.86–90.54)	
Proportion of patients alive in the mCRPC health state			
Proportion of patients that have first progression Darolutamide + ADT arm	0.74	Beta (0.58- 0.87)	Section B.3.5
Proportion of patients that have second progression Darolutamide + ADT arm	0.71	Beta (0.56- 0.83)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Proportion of patients that have third progression Darolutamide + ADT arm	0.66	Beta (0.52- 0.78)	
Proportion of patients that have first progression ADT arm	0.87	Beta (0.63- 0.98)	
Proportion of patients that have second progression ADT arm	0.71	Beta (0.56- 0.84)	
Proportion of patients that have third progression ADT arm	0.64	Beta (0.50- 0.75)	
Subsequent treatments distribution darolutamide arm			
Subsequent treatments distribution darolutamide arm – no treatment/BSC	0.91	Beta (0.61-0.99)	Section B.3.5
Subsequent treatments distribution darolutamide arm – ADT	0.00	Beta (0–0)	
Subsequent treatments distribution darolutamide arm – abiraterone	0.07	Beta (0- 0)	
Subsequent treatments distribution darolutamide arm – enzalutamide	0.00	Beta (0.05- 0.08)	
Subsequent treatments distribution darolutamide arm – docetaxel	0.55	Beta (0- 0)	
Subsequent treatments distribution darolutamide arm – radium-223	0.34	Beta (0.44- 0.65)	
Subsequent treatments distribution	0.24	Beta (0.27- 0.40)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
darolutamide arm – cabazitaxel			
Subsequent treatments distribution darolutamide arm – bicalutamide	0.00	Beta (0.19- 0.29)	
Subsequent treatments distribution ADT arm			
Subsequent treatments distribution ADT arm – no treatment/BSC	0.45	Beta (0.36-0.54)	Section B.3.5
Subsequent treatments distribution ADT arm –ADT	0.00		
Subsequent treatments distribution ADT arm –abiraterone	0.42	Beta (0- 0)	
Subsequent treatments distribution ADT arm – enzalutamide	0.42	Beta (0.33- 0.50)	
Subsequent treatments distribution ADT arm –docetaxel	0.47	Beta (0.33- 0.50)	
Subsequent treatments distribution ADT arm –radium-223	0.28	Beta (0.38- 0.56)	
Subsequent treatments distribution ADT arm –cabazitaxel	0.16	Beta (0.22- 0.33)	
Subsequent treatments distribution ADT arm – bicalutamide	0.00	Beta (0.13- 0.19)	
Utilities			
Health states			
Utilities: MFS – darolutamide	0.813	Beta/multinormal (0.63–0.94)	Section B.3.4

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Utilities: MFS – ADT	0.813	Beta/multinormal (0.63 –0.94)	
Utilities: PPS	0.704	Beta/multinormal (0.55–0.83)	
SSE and AE disutility			
SSE and AE disutility – anaemia	-0.11900	Beta (-0.126- -0.178)	Section B.3.4
SSE and AE disutility –arthralgia	-0.07000	Beta (-0.066- -0.095)	
SSE and AE disutility – back pain	-0.06900	Beta (-0.065- -0.094)	
SSE and AE disutility –diarrhoea	-0.10300	Beta (-0.105- -0.149)	
SSE and AE disutility – fatigue	-0.13100	Beta (-0.143- -0.200)	
SSE and AE disutility – hypertension	-0.15300	Beta (-0.176- -0.243)	
SSE and AE disutility – nausea	-0.04802	Beta (-0.043- -0.063)	
SSE and AE disutility – pain in extremity	-0.06900	Beta (-0.065- -0.094)	
SSE and AE disutility – urinary retention	-0.11000	Beta (-0.114- -0.162)	
SSE and AE disutility – urinary tract infection	-0.07000	Beta (-0.066- -0.095)	
SSE and AE disutility – spinal cord compression	-0.23700	Beta (-0.333- -0.439)	
SSE and AE disutility – pathological bone fracture	-0.20100	Beta (-0.259- -0.349)	
SSE and AEs durations			
Anaemia – duration in days	10.50	Normal (8.44-12.5)	Section B.3.5

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Arthralgia – duration in days	10.50	Normal (8.44-12.5)	
Back pain – duration in days	10.50	Normal (8.44-12.5)	
Diarrhoea – duration in days	10.50	Normal (8.44-12.5)	
Fatigue – duration in days	91.25	Normal (73.3-109.)	
Hypertension – duration in days	10.50	Normal (8.44-12.5)	
Nausea – duration in days	10.50	Normal (8.44-12.5)	
Pain in an extremity – duration in days	10.50	Normal (8.44-12.5)	
Urinary retention – duration in days	10.50	Normal (8.44-12.5)	
Urinary tract infection –duration in days	10.50	Normal (8.44-12.5)	
Spinal cord compression - duration in days	30.42	Normal (24.4-36.3)	
Pathological bone fracture – duration in days	30.42	Normal (24.4-36.3)	
SSE and AE rates darolutamide + ADT			
SSE and AE rates darolutamide – anaemia	0.01	Beta (0.00682-0.01010)	Section B.3.5
SSE and AE rates darolutamide – arthralgia	0.00	Beta (0.00255-0.00379)	
SSE and AE rates darolutamide – back pain	0.00	Beta (0.00341-0.00505)	
SSE and AE rates Darolutamide – diarrhoea	0.00	Beta (0- 0)	
SSE and AE rates darolutamide – fatigue	0.00	Beta (0.00341-0.00505)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
SSE and AE rates darolutamide – hypertension	0.03	Beta (0.02557-0.03789)	
SSE and AE rates darolutamide – nausea	0.00	Beta (0.00170-0.00252)	
SSE and AE rates darolutamide – pain in an extremity	0.00	Beta (0- 0)	
SSE and AE rates darolutamide – urinary retention	0.02	Beta (0.01279-0.01894)	
SSE and AE rates darolutamide – urinary tract infection	0.01	Beta (0.00511-0.00758)	
SSE and AE rates darolutamide – spinal cord compression	0.00	Beta (0.00170-0.00252)	
SSE and AE rates darolutamide – pathological bone fracture	0.00	Beta (0- 0)	
SSE and AE rates ADT			
SSE and AE rates ADT – anaemia	0.0036	Beta (0.00293-0.00435)	Section B.3.4
SSE and AE rates ADT – arthralgia	0.0036	Beta (0.00293-0.00435)	
SSE and AE rates ADT – back pain	0.0018	Beta (0.00146-0.00217)	
SSE and AE rates ADT – diarrhoea	0.0018	Beta (0.00146-0.00217)	
SSE and AE rates ADT – fatigue	0.0090	Beta (0.00734-0.01087)	
SSE and AE rates ADT – hypertension	0.0217	Beta (0.01761-0.02610)	
SSE and AE rates ADT – nausea	0.0000	Beta (0- 0)	
SSE and AE rates ADT–pain in an extremity	0.0018	Beta (0.00146-0.00217)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
SSE and AE rates ADT–urinary retention	0.0199	Beta (0.01615-0.02392)	
SSE and AE rates ADT–urinary tract infection	0.0054	Beta (0.00440-0.00652)	
SSE and AE rates ADT–spinal cord compression	0.0018	Beta (0.00146-0.00217)	
SSE and AE rates ADT–pathological bone fracture	0.0018	Beta (0.00146-0.00217)	
SSE and AEs unit costs			
SSE and AE unit costs –anaemia	£2,337.50	Gamma (1901-2817)	Section B.3.5
SSE and AE unit costs –arthralgia	£377.51	Gamma (307.-455.)	
SSE and AE unit costs –back pain	£377.51	Gamma (307.-455.)	
SSE and AE unit costs –diarrhoea	£477.21	Gamma (388.-575.)	
SSE and AE unit costs –fatigue	£348.49	Gamma (283.-420.)	
SSE and AE unit costs –hypertension	£338.57	Gamma (275.-408.)	
SSE and AE unit costs –nausea	£477.21	Gamma (388.-575.)	
SSE and AE unit costs –pain in an extremity	£377.51	Gamma (307.-455.)	
SSE and AE unit costs –urinary retention	£2,156.91	Gamma (1754-2599)	
SSE and AE unit costs –urinary tract infection	£2,652.37	Gamma (2158-3196)	
SSE and AE unit costs –spinal cord compression	£6,184.46	Gamma (5031-7454)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
SSE and AE unit costs –pathological bone fracture	£3,752.41	Gamma (3053-4522)	
Unit costs resource use			
Terminal cost – one-off	£7,760.62	Gamma (6314-9353)	Section B.3.5
Unit cost – outpatient visit – consultant	£109.00	Gamma (88.6-131.)	
Unit cost – outpatient visit – nurse	£38.00	Gamma (30.9-45.8)	
Unit cost – community nurse visit	£37.00	Gamma (30.1-44.5)	
Unit cost – A&E visit	£168.33	Gamma (136.-202.)	
Unit cost – CT scan	£115.56	Gamma (94.0-139.)	
Unit cost – bone scan	£271.30	Gamma (220.-326.)	
Unit cost – full blood count	£2.79	Gamma (2.26-3.35)	
Unit cost – liver function test	£1.10	Gamma (0.89-1.32)	
Unit cost – kidney function test	£1.10	Gamma (0.89-1.32)	
Unit cost – PSA count	£1.10	Gamma (0.89-1.32)	
Unit cost – testosterone test	£1.10	Gamma (0.89-1.32)	
Unit cost – metabolic panel/ biochemistry	£1.10	Gamma (0.89-1.32)	
Unit cost – blood and electrolytes	£1.10	Gamma (0.89-1.32)	
Unit cost – bone profile	£131.01	Gamma (106.-157.)	
Unit cost – X-ray	£30.59	Gamma (24.8-36.8)	
Unit cost – inpatient hospitalizations-day case	£751.90	Gamma (611.-906.)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Unit cost – inpatient hospitalizations – overnight admission	£1,707.93	Gamma (1389-2058)	
Unit cost – inpatient hospitalizations – overnight admission excess bed	£399.00	Gamma (324.-480.)	
Frequency per cycle – resource use nmCRPC state			
Frequency per cycle nmCRPC state – outpatient visit – consultant	[redacted]	[redacted]	Section B.3.5
Frequency per cycle nmCRPC state – outpatient visit – nurse	[redacted]	[redacted]	
Frequency per cycle nmCRPC state – community nurse visit	[redacted]	[redacted]	
Frequency per cycle nmCRPC state – A&E visit	[redacted]	[redacted]	
Frequency per cycle nmCRPC state – CT scan	[redacted]	[redacted]	
Frequency per cycle nmCRPC state – bone scan	[redacted]	[redacted]	
Frequency per cycle nmCRPC state – full blood count	[redacted]	[redacted]	
Frequency per cycle nmCRPC state – liver function test	[redacted]	[redacted]	
Frequency per cycle nmCRPC state – kidney function test	[redacted]	[redacted]	
Frequency per cycle nmCRPC state – PSA count	[redacted]	[redacted]	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Frequency per cycle nmCRPC state – testosterone test	[redacted]	[redacted]	
Frequency per cycle nmCRPC state – metabolic panel/ biochemistry	[redacted]	[redacted]	
Frequency per cycle nmCRPC state – blood and electrolytes	[redacted]	[redacted]	
Frequency per cycle nmCRPC state – bone profile	[redacted]	[redacted]	
Frequency per cycle nmCRPC state – X-ray	[redacted]	[redacted]	
Frequency per cycle nmCRPC state – inpatient hospitalizations – day case	[redacted]	[redacted]	
Frequency per cycle nmCRPC state – inpatient hospitalizations – overnight admission nmCRPC/mCRPC	[redacted]	[redacted]	
Number of days in hospital	[redacted]	[redacted]	
NHS average number of stay for elective patient stay	[redacted]	[redacted]	
Frequency per cycle mCRPC state – Outpatient visit – consultant	[redacted]	[redacted]	Section B.3.5
Frequency per cycle mCRPC state –	[redacted]	[redacted]	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
outpatient visit – nurse			
Frequency per cycle mCRPC state – community nurse visit	[redacted]	[redacted]	
Frequency per cycle mCRPC state – A&E visit	[redacted]	[redacted]	
Frequency per cycle mCRPC state – CT scan	[redacted]	[redacted]	
Frequency per cycle mCRPC state – bone scan	[redacted]	[redacted]	
Frequency per cycle mCRPC state – full blood count	[redacted]	[redacted]	
Frequency per cycle mCRPC state – liver function test	[redacted]	[redacted]	
Frequency per cycle mCRPC state – kidney function test	[redacted]	[redacted]	
Frequency per cycle mCRPC state – PSA count	[redacted]	[redacted]	
Frequency per cycle mCRPC state – testosterone test	[redacted]	[redacted]	
Frequency per cycle mCRPC state – metabolic panel/ biochemistry	[redacted]	[redacted]	
Frequency per cycle mCRPC state –	[redacted]	[redacted]	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
blood and electrolytes			
Frequency per cycle mCRPC state – bone profile	[redacted]	[redacted]	
Frequency per cycle mCRPC state – X-ray	[redacted]	[redacted]	
Frequency per cycle mCRPC state – inpatient hospitalizations – day case	[redacted]	[redacted]	
Frequency per cycle mCRPC state – inpatient hospitalizations – overnight admission nmCRPC/mCRPC	[redacted]	[redacted]	
Number of days in hospital	[redacted]	[redacted]	
Curve fit parameters (OS) – Weibull			
Curve fit parameter OS: Rate – darolutamide + ADT	0.408352189	Multinormal distribution	Section B.3.3
Curve fit parameter OS: Scale – darolutamide + ADT	8.123769792		
Curve fit parameter OS: Rate – ADT	0.637737683		
Curve fit parameter OS: Scale – ADT	7.625386861		
Curve fit parameters (PFS) – Weibull			
Curve fit parameter MFS: Rate – darolutamide + ADT	0.359115182	Multinormal distribution	Section B.3.3
Curve fit parameter MFS: Scale – darolutamide + ADT	7.419366927		

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Curve fit parameter MFS: Rate – ADT	0.322609867		
Curve fit parameter MFS: Scale – ADT	6.702577076		
Curve fit parameters (ToT) – Gompertz			
Curve fit parameter ToT: Rate	[redacted]	Multinormal distribution	Section B.3.3
Curve fit parameter ToT: Scale	[redacted]	Multinormal distribution	
Key: 1L, first-line; 2L, second-line; 3L, third-line; ADT, androgen deprivation therapy; AEs; adverse events; A&E, accident and emergency; CI, confidence interval; CT, computerized tomography; IV, intravenous; mCRPC, metastatic castration-resistant prostate cancer; MFS, metastasis-free survival; nmCRPC, non-metastatic castration-resistant prostate cancer; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; PSA, prostate specific antigen; SSE, symptomatic skeletal events; ToT, time on treatment.			

Assumptions

A summary of key model assumptions for the model base case is detailed in Table 48.

Table 48: Key model assumptions

Assumption	Assumption–description	Justification
Time horizon	27 years reflects a lifetime horizon for patients with nmCRPC	At 27 years in the model, using ARAMIS patient data, patients in all arms reach 100 years old. The impact of varying the time horizon on the results was tested in scenario analysis

Assumption	Assumption–description	Justification
Darolutamide and ADT MFS curve	Independently fitted Weibull distributions accurately reflect the expected MFS of nmCRPC patients over time	The Weibull curve was selected for the base case for both arms as it had a good visual and statistical fit (based on the AIC and BIC statistics) and provided the most plausible extrapolation according to clinicians (3) Alternative plausible parametric survival curves were explored in scenario analysis
Darolutamide and ADT OS curve	Independently fitted Weibull distributions accurately reflect the expected OS of nmCRPC patients over time	
Subsequent treatment distribution and the proportion of patients alive expiring first, secondary and tertiary progression	Estimates from the advisory board	Subsequent treatment distribution sourced from the clinical validation meeting were used in the base case as they are reflective of the current UK clinical practice Alternative subsequent treatment distributions based on ARAMIS and TA580 (76) were explored in scenario analyses. The average number of patients experiencing a first, secondary and tertiary progression was estimated from the model based on the proportion of patients alive at time of progression at each line per arm. The time of experiencing the first progression was approximated by the undiscounted mean MFS LYs for each arm. As for the time of the secondary and tertiary progressions, these were estimated based on a weighted average duration that a patient would spend in the previous lines using the distribution at each line and the mean treatment durations sourced from published literatures (58, 59, 97).

Assumption	Assumption–description	Justification
Utility values in nmCRPC	Health state utilities are assumed to be the same for both treatment arms and reflected by the HRQL of patients from ARAMIS	The treatment arm covariate was not found to be significant in ARAMIS trial data analysis. This was excluded in the model base case to avoid double counting of the impact of AEs and SSEs disutilities
Utility values in mCRPC	A weighted average mCRPC utility was used	Utility values for mCRPC from ARAMIS were based on a small sample size and were not reflective of the whole mCRPC health state, as most data were collected in the early stage of mCRPC. As suggested in the clinical validation meeting, a weighted average utility for the mCRPC state was estimated based on the mean time spent in each line of therapy in the mCRPC states (3).
ADT distribution	ADT distribution	Based on clinical opinion from the model validation meeting and in line with the ARAMIS trial protocol, a blended basket of common ADT treatments, including leuprorelin (40%), goserelin (30%), triptorelin (20%) and buserelin (10%), was used to represent the ADT arm in the model.
Healthcare resource use frequencies	Healthcare resource use for nmCRPC and mCRPC patients is reflective of the outcomes from the IQVIA study	As no healthcare resource use utilization frequencies were reported for patients in the nmCRPC state in the UK, Bayer funded a study led by IQVIA to understand healthcare resource use in nmCRPC patients prior to and following occurrence of metastasis in the UK

Assumption	Assumption–description	Justification
The patient population from ARAMIS is reflective of patients from UK clinical practice	Patients' characteristics from ARAMIS are similar to that of the UK nmCRPC patient population The inclusion of 5% and 7% of metastatic patients does not change the comparability of the ARAMIS trial population to that of UK clinical practice, and the BMC analysis performed minimizes the impact of these patients	Clinicians found the patient population representative of UK patients seen in clinical practice (3). In the model base case, the BMC was chosen on the basis that primary MFS analysis in the ARAMIS trial was based on metastases identified by blinded central review (not by investigators), and exclusion criteria for ARAMIS prohibit patients with metastases at baseline. This was further accepted by the clinical experts (3).
Key: ADT, androgen deprivation therapy; AEs, adverse events; AIC, Akaike information criterion; BIC, Bayesian information criterion; BMC, baseline metastases censored; HRQL, health-related quality of life; mCRPC, metastatic castration-resistant prostate cancer; MFS, metastasis-free survival; nmCRPC, non-metastatic castration-resistant prostate cancer; OS, overall survival; SSEs, symptomatic skeletal events.		

B.3.7. Base case results

Base case incremental cost-effectiveness analysis results

The base case discounted cost-effectiveness results with PAS are presented in Table 49. Using a 27-year time horizon, the incremental life years associated with darolutamide versus ADT were 2.37. The discounted incremental costs of £21,374 and incremental QALYs of 1.87 resulted in an ICER of £11,445 versus ADT. This is well below the range that NICE usually considers to be cost effective of £20,000-£30,000. Furthermore, with an incremental MFS life year gain of 1.81 for darolutamide, the cost per MFS month gained versus ADT is £986.

Table 49: Base case results: darolutamide (with PAS) + ADT versus ADT (list price)

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]	£21,374	2.37	1.87	1.81	£11,445	£986

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.

B.3.8. Sensitivity analyses

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was undertaken to explore the uncertainty of all model parameters and their associated impact on cost-effectiveness results. To ensure convergence, 2,000 iterations were used. The total costs, life years and QALYs were recorded for each iteration and averaged.

The probabilistic results presented in Table 50 are consistent with the results from the deterministic analysis (see Table 49) in terms of the total costs, QALYs and life years associated with each treatment.

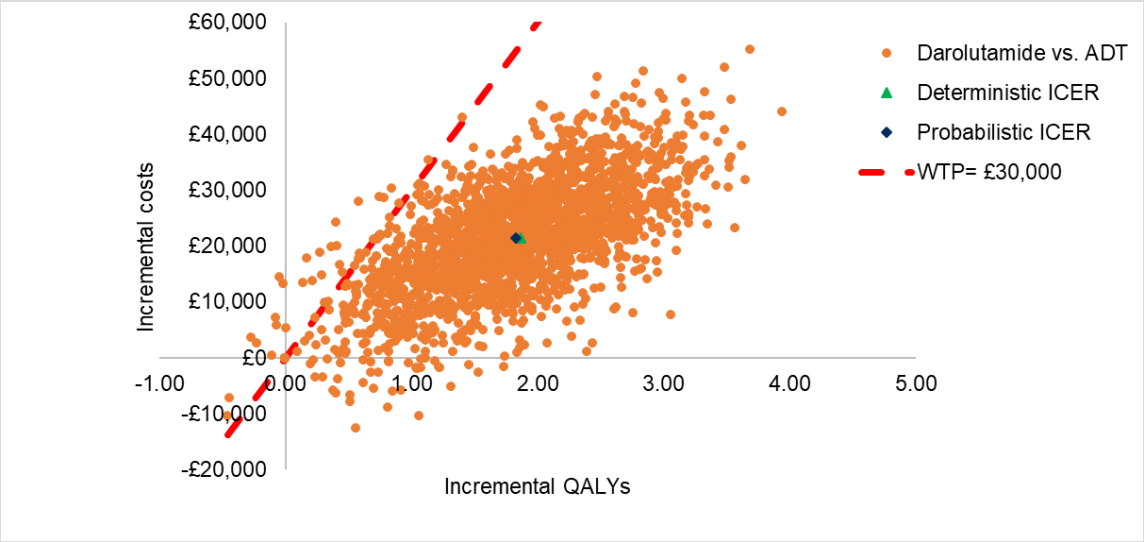
Table 50: Probabilistic results: darolutamide (with PAS) + ADT versus ADT (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
ADT	[redacted]	[redacted]	[redacted]				
Darolutamide + ADT	[redacted]	[redacted]	[redacted]	£21,466	2.31	1.83	£11,758

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

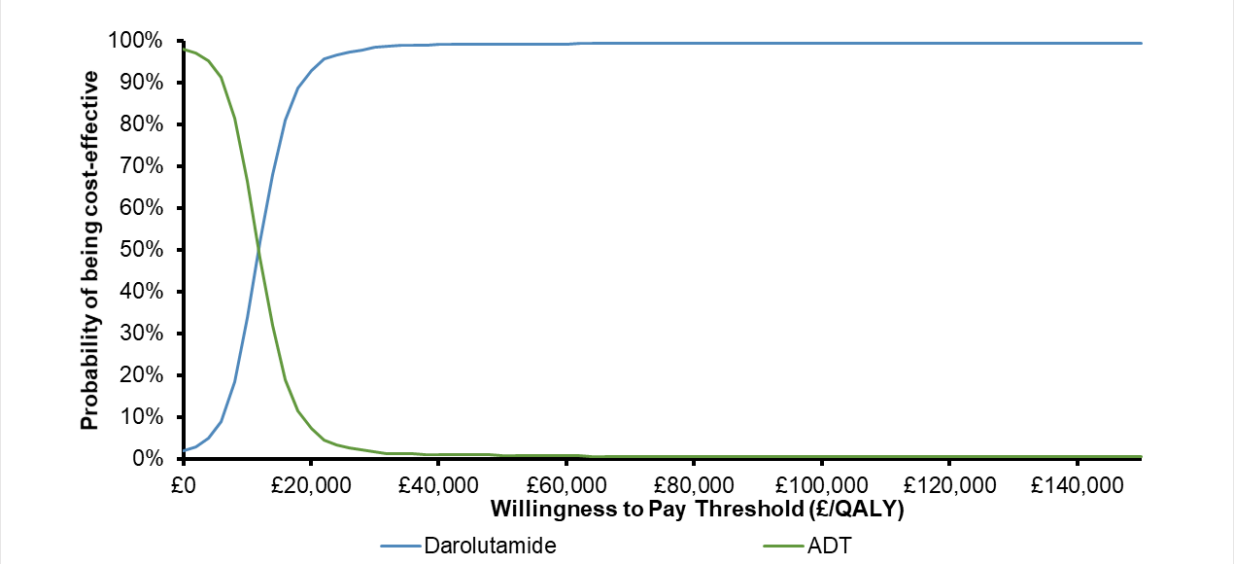
Figure 26 represents the scatter plot of the incremental costs and QALYs from the probabilistic sensitivity analysis results based on 2,000 iterations. As shown in the cost-effectiveness acceptability curve (Figure 27), darolutamide has a 98.35% probability of being cost effective versus ADT, considering the £30,000 willingness to pay threshold.

Figure 26: Cost-effectiveness plane – darolutamide (with PAS) applied versus ADTs (at list price)



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

Figure 27: Cost-effectiveness acceptability curve – darolutamide (with PAS) versus ADTs (at list price)

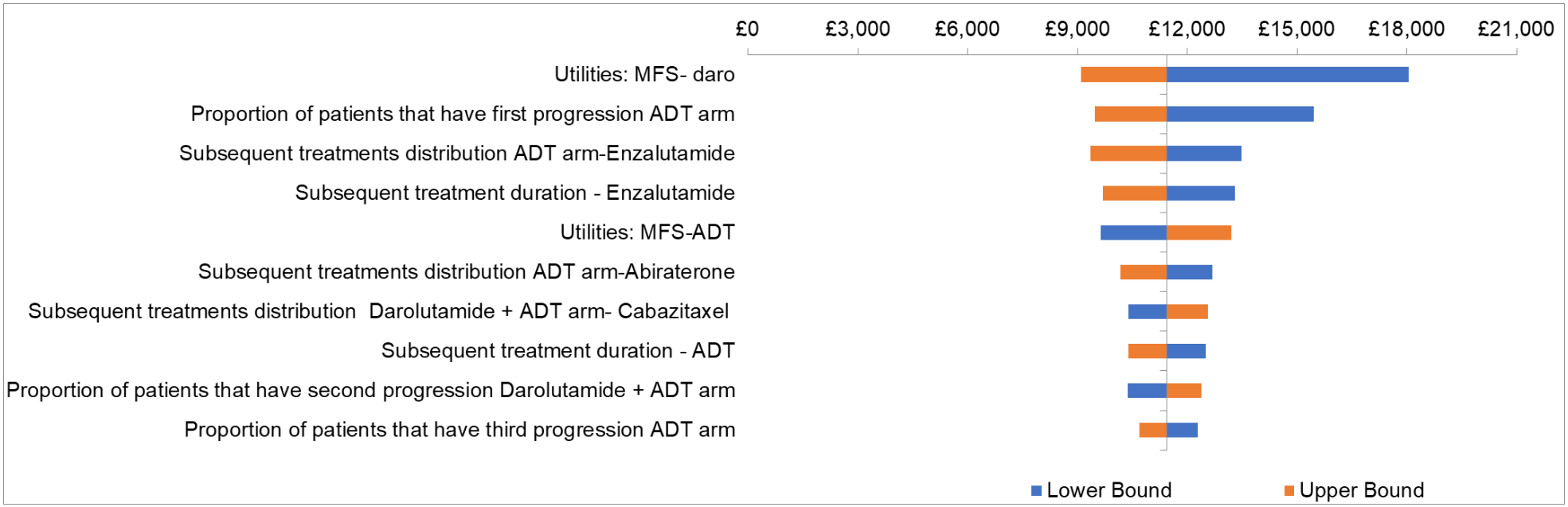


Key: ADT, androgen deprivation therapy; PAS, patient access scheme.

Deterministic sensitivity analysis

One-way sensitivity analyses were performed by varying each parameter between its upper and lower bound values. The upper and lower bound values were taken from 95% confidence intervals or estimated based on standard errors and sample size if these data were available (see in Table 47 Section B.3.6). In the absence of these data, the standard error was assumed to be 10% of the mean value. Tornado diagrams presenting the 10 parameters with the biggest impact on the ICER for darolutamide versus ADT are shown in Figure 28. The parameters that had the biggest impact on the cost-effectiveness results versus ADT were the utility values used for MFS, the proportion of patients experiencing a first progression followed by the proportion of patients receiving enzalutamide on the ADT arm. Remaining model parameters did not have a big impact on the ICER.

Figure 28: Tornado diagram (ICER) darolutamide (with PAS) versus ADT plus (list price)



Key: ADT, androgen deprivation therapy; ICER, incremental cost-effectiveness ratio; MFS, metastasis-free survival; PAS, patient access scheme; daro, darolutamide.

Scenario analysis

Table 51 presents the list of scenario analyses conducted. Assumptions regarding alternative parametric curve models to model ToT and source of subsequent treatment distribution following disease progression have the largest impact on cost-effectiveness results and conclusions. Other scenarios explored had limited impact on the cost-effectiveness results and conclusions. In all of the presented scenarios, the resulting ICER was always below the willingness to pay threshold of £30,000.

Table 51: Summary table of scenario analyses settings and results

	Scenario description	Base case setting	Scenario setting	Results
1	Base case			£11,445
2	Baseline metastasis censoring assumption	MFS BMC	MFS BME	£10,207
3	OS extrapolation (darolutamide and ADT arms)	Weibull	Log-logistic	£11,810
4			Log-normal	£12,478
5	MFS extrapolation (darolutamide and ADT arms)	Weibull	Generalized gamma	£12,879
6			Log-logistic	£10,701
7			Log-normal	£9,162
8	ToT extrapolation (darolutamide + ADT arm)	Gompertz	Generalized gamma	£13,651
9			Weibull	£13,804
10			Log-logistic	£16,100
11			Log-normal	£16,814
12	Long term OS assumption for ADT (cut off for assuming same mortality risk as darolutamide)	No cut-off	8.7 years	£11,729
13	nmCRPC utilities	BMC without differentiation by treatment arm	Separate BMC with differentiation by treatment arm	£11,336

	Scenario description	Base case setting	Scenario setting	Results
14	mCRPC utilities	Weighted average utility	NICE TA412	£11,289
			BMC with differentiation by treatment arm	£11,743
15	Subsequent treatment	Average from the clinical validation meeting	ARAMIS – first-line	£25,377
16			ARAMIS – all lines	£25,797
17			NICE TA580 – average (CDF & ERG)	£15,214
18	Time horizon	27 years	10 years	£11,875
19			20 years	£11,426
20	Half-cycle correction	Included	Excluded	£11,642
21	Drug wastage	Included	Excluded	£11,060
22	Healthcare resource use frequency source	IQVIA study	TA580	£9,311

Key: ADT, androgen deprivation therapy; BMC, baseline metastases censored; BME, baseline metastases counted as events; CDF, Cancer Drugs Fund; ERG, evidence review group; mCRPC, metastatic castration-resistant prostate cancer; MFS, metastasis-free survival; nmCRPC, non-metastatic castration-resistant prostate cancer; OS, overall survival; ToT, time on treatment.

Summary of sensitivity analyses results

Uncertainties around cost-effectiveness results were extensively explored through various probabilistic and deterministic sensitivity analyses (one-way sensitivity analyses and scenario analyses).

One of the main uncertainties in the model is the immaturity of OS data. As such, various parametric functions with a good fit to the data were tested to explore the effect of structural uncertainties on the ICER. The majority of scenarios resulted in a marginally higher ICER estimate. Similarly, when a conservative 8.7-year cut-off point was tested around the assumption of when the mortality risk in the ADT arm is the same as the darolutamide + ADT arm, the scenario resulted in only a small increase in the ICER. The only scenarios that resulted in a significant increase in the ICER were that where subsequent treatment distribution from TA580 and ARAMIS trial were selected, and where alternative time on darolutamide treatment extrapolation methods were used. The increase in ICER with subsequent treatment scenarios is a result of the relatively short follow-up of the ARAMIS trial compared with the expected long-term mCRPC health state. The subsequent treatments observed in the ARAMIS trial are not representative of subsequent treatments for managing mCRPC in the UK, especially in later lines, as informed by a panel of leading expert clinicians (3). The scenarios testing alternative ToT extrapolations use log-normal and log-logistic curves, which did not have a statistically good fit relative to other curves and also resulted in an implausible number of patients on treatment in the long-term because of the flat tails resulting in >20% of patients on treatment at 10 years. Changes to the assumptions around utilities, drug wastage, healthcare resource use, metastatic patient censoring, MFS, OS and long-term OS all resulted in minimal changes to the ICER.

In addition, the one-way sensitivity analysis indicated that the most influential drivers of the model were related to MFS utility values used for MFS, the proportion of patients experiencing a first progression followed by the proportion of patients receiving enzalutamide on the ADT arm. The probabilistic sensitivity analysis demonstrated that there was a 98.35% probability of darolutamide being cost effective at a willingness to pay threshold of £30,000/QALY.

B.3.9. Subgroup analysis

No subgroup analysis has been conducted.

As part of the other considerations in the NICE final scope, it was detailed that if evidence allows, a subgroup analysis by PSADT will be considered (63). As the ARAMIS trial was not statistically powered to detect differences in these subgroups, we did not consider it appropriate to conduct any such analyses. Subgroup analyses using Cox regression models were conducted on MFS and showed very similar results between PSADT, PSA level at baseline and PSA level at baseline relative to median subgroups (Section B.2.7), hence no meaningful differences in the cost-effectiveness results are expected within these subgroups (1).

B.3.10. Validation

Validation of cost-effectiveness analysis

Outcomes from relevant clinical trials and TA580 are presented alongside the predicted PFS and OS from the model in Appendix J.

The model estimates darolutamide median MFS at 3.60 years, comparable to the median 3.37 years reported in the ARAMIS trial. For the ADT arm, the model provides estimated median MFS close to the reported median MFS in the ARAMIS trial (1.76 years versus 1.84 years). Although median OS was not reached in the ARAMIS trial or any of the published nmCRPC trials (ARAMIS, SPARTAN and PROSPER), clinical experts suggested that long-term extrapolations from the model are in line with what is expected to be seen in clinical practice. In addition, analyses from the latest data cut from ARAMIS will be included in the cost-effectiveness model when available; updated results will be provided to NICE at the earliest opportunity.

Quality control

The model went through an extensive quality check by a health economist not involved in the model's construction. They reviewed the model for coding errors,

inconsistencies and the plausibility of inputs. The model was also put through a checklist of known modelling errors and all modelling assumptions were questioned.

Clinical experts' validation

Validation of the model assumptions and outcomes was conducted at an advisory board on 4 February 2020 comprising ten leading UK practicing clinicians (3).

The clinical experts confirmed that the baseline characteristics of ARAMIS trial are aligned with what they would expect to see in UK clinical practice and so they consider these data to be reflective of the UK population.

The group suggested that using one state to depict the mCRPC disease progression state does not allow the model to fully capture the difference in the QoL at each metastatic progression state. However, it was agreed that the current model structure is most appropriate given the availability of trial and publicly available data. A weighted average utility for the mCRPC health state was suggested and incorporated in the model to overcome the simple three-state modelling approach by capturing the differences in the QoL in the mCRPC state.

The clinical experts agreed that although in clinical practice some metastatic patients would be missed, for the purpose of the cost-effectiveness analyses it is more conservative to censor patients with metastasizes at baselines to avoid confounding the analyses (3). As such, the BMC analyses were used in the model base case.

The extrapolated OS, MFS and ToT curves, based on the ARAMIS for both the darolutamide + ADT and ADT arms, were validated in the clinical validation meeting. Clinical experts agreed that the Weibull curve for the OS and MFS in both arms were a reasonable choice and resulted in the most clinically plausible long-term extrapolations. Although one clinical expert suggested that based on previous clinical trials it is possible for patients to stay on active treatment for 15 years, and another argued that it would be best to choose the Weibull for consistency between all endpoints, the majority of clinical experts commented that the best model lies in between the Weibull and Gompertz, but supported the use of Gompertz in the base case as it does result in clinically plausible long-term extrapolation for darolutamide

ToT. As for the ADT arm, they confirmed that in line with the UK clinical practice ADT is given to patients across the nmCRPC and mCRPC time horizon. As suggested by the experts, the basket of ADT treatment consisted of leuprorelin (40%), goserelin (30%), triptorelin (20%) and buserelin (20%) (3).

Regarding the mCRPC utility, clinical experts suggested using a weighted average utility that lies between 0.6–0.7 for the mCRPC state is more reflective of the QoL of patients in this state compared to QoL sourced from TA412, as the latter is reflective of patients later in the mCRPC state where radium-223 is offered. This further supports the estimated 0.704 mCRPC utility used in the model base case.

In order to estimate the subsequent treatment distribution for the mCRPC state that is reflective of the UK clinical practice, clinical experts were split into two groups and asked to provide the expected distribution of subsequent treatments for each arm. Both workshop groups came to a similar consensus regarding the proportion of subsequent treatments post-metastatic progression on darolutamide + ADT and ADT arms.

B.3.11. Interpretation and conclusions of economic evidence

Comparison with published economic literature

The model base case results reflect the cost-effectiveness of darolutamide versus ADT in high-risk nmCRPC patients. The model estimates median MFS for darolutamide to be to be 3.6 years versus 1.76 years for ADT. These estimates align with the observed median MFS in ARAMIS (3.37 years and 1.84 years, respectively). Median OS in the model base case was estimated at 7.21 years for darolutamide and 4.60 years for ADT.

In the base case analysis, it was estimated that the total QALYs for darolutamide were [redacted] with the estimated total cost of [redacted]. For ADT, the base case analysis estimated [redacted] total QALYs, with a total cost of [redacted]. This results in an ICER of £11,445/QALY. Overall, model results were sensitive to the assumptions of the ToT extrapolation in both arms and the source of the subsequent treatment distribution, resulting in an increase that ranges between £13,653 and £28,800 in the ICER.

This evaluation considers all patients identified in the decision problem.

Generalizability of the analysis

Clinical expert opinion confirmed that the data from the ARAMIS trial are aligned with what they would expect to see in UK clinical practice (3). Therefore, we consider these data generalizable to the UK population.

The model was developed using NHS reference costs and costs from previous technology appraisals presented to NICE. These cost inputs are considered to be the most appropriate choice to model the cost-effectiveness of darolutamide in the UK population.

In summary, all steps have been taken to produce a robust and conservative estimate of the clinical and cost-effectiveness of darolutamide, reflective of UK clinical practice.

Strength of the economic evaluation

The economic analysis optimizes the use of the available data in this patient population, while fully accounting for the clinically and economically relevant parameters in the decision problem.

Model structure and assumptions were based on the accepted approaches presented in TA580 and were further validated by clinical and health economic experts (3, 57). Key model assumptions and uncertainties were extensively explored through sensitivity analyses. In all of the alternative scenarios presented, darolutamide remained cost effective compared with ADT at a willingness to pay threshold of £30,000 per QALY gained.

Limitations of the economic evaluations

The key limitation of the analysis is the immature OS data from the ARAMIS trial. Consequently, there is greater uncertainty in the longer-term OS, in terms of absolute OS and its comparative benefits, versus ADT. Given the uncertainty, assumptions were explored including assuming the mortality risk of ADT to be the

same as darolutamide after a certain cut-off point (8.7 years assumed in the scenario analysis) which had a minimal impact on results.

Given the nature of the metastatic disease progression of the mCRPC state, the current three-state model structure may oversimplify disease progression. However, this chosen structure was considered to be appropriate by the clinicians in the advisory board (3) given the availability of trial and publicly accessible data. Furthermore, it was agreed that splitting the mCRPC state by line of therapies will introduce significant uncertainty to the cost-effectiveness model given that data will be based on external trials. This is also in line with the committee and Evidence Review Group's (ERG) opinion in TA580 (2), where they expressed concerns about the proposed sequence and transition estimates between the progressed states of the company's model. However, to overcome the oversimplistic model structure, the costs and utility associated with each subsequent treatment line is accounted for within the mCRPC health state (please refer to Sections B.3.4 and B.3.5. for more details).

Although EQ-5D-3L data were collected in the ARAMIS trial, the majority of the data were collected before metastatic progression due to the trial design, the relatively short trial follow-up period and relatively long time that patients stay in the nmCRPC health state, especially patients in the darolutamide + ADT arm. Therefore, utility values for the mCRPC health state were estimated based on few records (most of which were recorded soon after the metastasis progression event) and may not be representative of health utilities for the entire mCRPC health state, especially towards the later stage of mCRPC. As such a weighted average utility for the mCRPC state was estimated based on the time spent in each line of therapy, sourced from TA377 and TA580 (2, 58).

Furthermore, given the double-blind nature of the ARAMIS trial and the relative short follow-up compared with the expected long-term mCRPC health state, the subsequent treatments observed in the ARAMIS trial do not accurately represent the subsequent treatments used to manage mCRPC in UK clinical practice, especially in

later lines. Therefore, subsequent treatments for mCRPC were based on the clinical experts' opinion gained at the validation meeting.

Further analysis

Analysis is currently underway of the new data cut from ARAMIS (15 November 2019), with a more mature and statistically significant OS as well as more mature ToT data. However, as this is being performed at a stage where the analyses included in the economic model have already been finalized, it was not feasible to update the economic results using the recently available OS and ToT data with the scheduled submission date. Bayer will provide an update to the analyses presented in this submission at the earliest available opportunity.

Conclusion

The presented economic model provides robust evidence of the cost-effectiveness of darolutamide versus ADT in the treatment of high-risk nmCRPC patients. It was estimated that darolutamide is associated with higher QALYs and life years gains compared with ADT when considering a lifetime horizon, therefore providing potential to be a cost-effective treatment option. This is especially important for a population of patients with high unmet needs, where no targeted therapies are currently approved in the NHS. Despite the immature OS data and the uncertainties around the long-term extrapolation for the trial outcomes (MFS, OS and ToT), through the various sensitivity analyses darolutamide was cost effective versus ADT in 98.35% of the PSA iterations and remained below the willingness to pay threshold of £30,000 in all the tested alternative scenarios. Moreover, long-term extrapolation of survival outcomes and various modelling assumptions were extensively validated by clinical experts and by a health economic expert (3, 57). As a result we can conclude that darolutamide offers a cost effective treatment option for high-risk nmCRPC patients in the UK – a patient population with a high level of unmet need.

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B.5. Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Analyses of baseline metastases counted as events at Day 0

Appendix L: Threshold analysis

Appendix M: Checklist of confidential information

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Clarification questions

March 2020

File name	Version	Contains confidential information	Date
ID1443 Clarification questions to PM for company_redacted v1.1	V 1.1	No	03.07.2020

Section A: Clarification on effectiveness data

Methods used to assess the main clinical effectiveness evidence

A1. Document B, section B.2.5 and Appendix D.3. These sections of the company submission refer to the quality assessment of the ARAMIS study. Please clarify how many reviewers carried out the risk of bias assessment of the study and whether they worked independently.

The risk of bias assessment of all included studies was performed as a part of the data extraction process and therefore, the same approach was applied, i.e. one reviewer independently extracted the data and performed the risk of bias assessment of all studies and another reviewer independently checked the assessment against the source publications.

Primary and secondary efficacy outcomes

A2. PRIORITY. Document B, Figures 5, 6 and 11, pages 48 – 60. Please supply the time to event data for metastasis free survival, overall survival and time to initiation of subsequent antineoplastic therapy that is, the raw data underpinning the Kaplan Meier curves.

Unfortunately, we do not have permission to share the patient level data, that is the time to event raw data underpinning the Kaplan Meier curves. If there are specific analyses that need to be conducted on the raw data Bayer can run these and share the outputs.

A3. PRIORITY. Document B, page 53. If possible, please provide the results for overall survival analysis using the most recent data-cut from 15th November 2019. If not, please clarify when these data are expected to be available?

At the time of the primary analysis, (data cut-off 3rd September 2018), only 136 out of the 240 overall survival (OS) events planned for the final OS analysis had occurred. Thus, in our original submission, we submitted results of an interim analysis of OS, stating that this would be updated once the final analysis was available.

A total of [redacted] events had occurred in the final analysis (data cut-off 15th November 2019). Based on a pre-specified alpha level of 0.0498, darolutamide + 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. An updated analysis of the mature time on treatment data from this final data-cut (15th November 2019) was also performed.

Please refer to the separately attached Appendix N which contains a clinical overview of the analyses from the final data-cut (15th November 2019) and a summary of the methods utilised in the analysis of the OS and ToT data as well as a detailed break-down of the results of the updated cost-effectiveness model.

In the ARAMIS trial, the OS endpoint was analysed using two crossover adjustment methods to account for patients in the ADT arm that crossed to the darolutamide + ADT arm during the trial. As a result, the ADT arm changes for each crossover analysis but the darolutamide arm stays the same. The two crossover algorithms considered were the iterative parameter estimate (IPE) and the Rank Preserving Structural Failure Time (RPSFT). Both algorithms are randomization based-methods and assume that the relative treatment effect for patients who crossed to the other treatment arm is the same as patients that were originally randomized to the intervention arm.[1] When using the November 2019 data-cut, the unadjusted analysis was used in the model base case. This was considered to be the most appropriate approach given the uncertainty introduced when applying any type of adjustment, and the small effect adjustment had on the KM data and subsequent survival analysis (Figure 2, Figure 3 and Figure 4). Moreover, as shown in Figure 1, using the unadjusted data is deemed to be the most conservative approach regarding ADT OS, with a marginally greater OS compared with the crossover adjustments. However, the crossover-adjusted analyses are included in the updated cost-effectiveness model and have been presented as sensitivity analyses.

Figure 1: KM and best fitted parametric survival models for unadjusted and crossover adjusted OS for the ADT arm

Figure 2: Parametric survival models for the unadjusted OS for the ADT arm

Figure 3: Parametric survival models for crossover adjusted OS (IPE method) for the ADT arm

Key: ADT; androgen deprivation therapy; IPE; iterative parameter estimate; OS, overall survival.

Figure 4: Parametric survival models for crossover adjusted OS (RPSFT method) for the ADT arm

Key: ADT; androgen deprivation therapy; RPSFT; Rank Preserving Structural Failure Time.

All scenarios in this document have been run using the September 2018 and November 2019 data-cut using the submitted company base case settings and updated company base case settings. The updated company base case uses the final November 2019 data-cut for the OS (unadjusted OS) and ToT and includes the amendments requested in B13 and B15 as well as the changes implemented to address the uncertainties raised in B4, B6 and B12. The impact of each of these individual changes is described in the responses to the corresponding questions. In addition, the updated company base case corrects two formulae inconsistencies in the "Subseq_TrT" cells E92-E93 and "Parameter" sheets cells D182-D183 and D202-D203.

The results using the September 2018 and November 2019 data-cuts are presented in Table 1. Using the more mature data-cut resulted in a significant decrease in the ICERs. Considering the crossover adjusted OS data for the ADT arm results in a moderate increase in the ICER; this is driven by lower OS for the ADT reducing the time spent in the costly post metastatic progression health state (when list prices are assumed for subsequent therapies), resulting in a smaller incremental cost (which is greater than the incremental QALY loss) and thereby a larger ICER.

Table 1: Results of the November 2019 data-cut

ARAMIS trial data-cut used	**Scenario**	**ICER (£/QALY): darolutamide +ADT versus ADT**
September 2018	Submitted company model base case	£11,455
	Updated company model base case	**£11,270**
November 2019 (OS and ToT)	Submitted company model base case (unadjusted OS)	£6,296
	Submitted company model – IPE crossover adjustment	£6,799
	Submitted company model – RPFST crossover adjustment	£6,602
	Updated company model base case (unadjusted OS)	**£4,919**
	Updated company model – IPE crossover adjustment	£5,763

ARAMIS trial data-cut used	Scenario	ICER (£/QALY): darolutamide +ADT versus ADT
	Updated company model – RPFST crossover adjustment	£5,433
Key: mCRPC, metastatic castration resistant prostate cancer; ICER, incremental cost-effectiveness ratio; OS, overall survival; ToT, time on treatment; ADT, androgen deprivation therapy.		

Subsequent anticancer therapy in patients who discontinued study treatment

A4. Document B, Table 15, page 61. The information reported in the table suggests that only 100 people in the darolutamide arm and 130 people in the placebo arm out of the 339 in the darolutamide arm and 354 in the placebo arm who discontinued the study treatment received an additional treatment. Please confirm this is correct. If not, please clarify how many patients who discontinued treatment received additional treatment other than cytotoxic chemotherapy and/or antineoplastic therapy, and also indicate what was the additional treatment.

The figures quoted in Document B, Table 15, page 61 are correct. As of the September 2018 data-cut, 100/339 patients in the darolutamide arm and 130/354 patients in the placebo arm who discontinued study treatment received subsequent cytotoxic chemotherapy and/or anti-neoplastic treatment. All patients, and study personnel, including clinicians, remained blinded to treatment assignments during the double-blind part of the study (i.e. until data cut-off for primary analysis, 3rd September 2018), hence, subsequent therapies reported here were selected without knowledge of whether the patient had received darolutamide or placebo as study therapy. The most common subsequent treatments were docetaxel (49% in the darolutamide arm and 50.8% in the placebo arm), abiraterone acetate (13% darolutamide arm and 17.7% placebo arm), and enzalutamide (18% darolutamide arm and 14.6% placebo arm).

Information on subsequent treatment use was collected up to the last data-cut of 15th November 2019 when 337 patients, 170 in the darolutamide arm and 167 in the

placebo arm, have received at least one subsequent treatment. A detailed break-down of all subsequent treatments received at the last data-cut is provided in Table 2 below.

Table 2: Subsequent use of cytotoxic chemotherapy and/or anti-neoplastic treatment (15th November 2019 data-cut)

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]
DOCETAXEL; PREDNISONE	[redacted]	[redacted]
DOXORUBICIN	[redacted]	[redacted]
EPIRUBICIN HYDROCHLORIDE	[redacted]	[redacted]
ETOPOSIDE	[redacted]	[redacted]
FLUOROURACIL	[redacted]	[redacted]
GOSERELIN ACETATE	[redacted]	[redacted]

Subsequent treatment **number patients taking treatment, n (%)**	**Darolutamide (n=170)**	**Placebo (n=167)**
IRINOTECAN HYDROCHLORIDE	[redacted]	[redacted]
METHOTREXATE	[redacted]	[redacted]
TEGAFUR	[redacted]	[redacted]
TRIPTORELIN ACETATE	[redacted]	[redacted]
TRIPTORELIN EMBONATE	[redacted]	[redacted]

Not all subsequent treatments received in ARAMIS are currently being used in UK clinical practice. However, enzalutamide, abiraterone, docetaxel and cabazitaxel were the most used subsequent treatments in ARAMIS, accounting for the vast majority of patients, and are also the most widely prescribed treatments in UK practice once patients progress to metastatic disease according to an expert panel of UK clinicians.[2] Based on clinical expert opinion the majority of patients would receive abiraterone/enzalutamide as first-line treatment once they progress on ADT alone. If darolutamide were to be recommended for use in nmCRPC, the majority of patients would receive docetaxel as first line once they progress. The double-blind nature of ARAMIS prevented investigators from knowing the treatment arm patients were randomised to, which can explain that roughly half of the patients in each arm were prescribed docetaxel based on the October 2018 data-cut. When looking at the November 2019 data-cut once investigators start to be unblinded, the docetaxel use in the darolutamide arm increases considerably as does the abiraterone and enzalutamide use in the placebo arm, which is in line with what would be expected in UK clinical practice. This suggests subsequent treatments in ARAMIS broadly reflect UK practice when accounting for the double-blind nature of the trial.

Section B: Clarification on cost-effectiveness data

B1. Document B, section B.3.3, page 106. In relation to the predicted overall survival estimates in the model using the Weibull distribution, please provide further evidence to support the statement "all experts agreed the predicted survival of the Weibull model at key time points (e.g. at 5 years, 10 years, 15 years, etc.) in the ADT arm closely matches what is currently observed in clinical practice, while the predicted survival in the darolutamide + ADT arm is in line with what the experts expect"

A clinical advisory board was organised by Bayer on 4th of February 2020 to validate the clinical assumptions used in the cost-effectiveness model and inform the subsequent treatment distribution that is currently being used in UK practice once patients progress to metastatic CRPC, but also how this distribution would change following the recommended use of darolutamide in the non-metastatic CRPC setting.[2] A representative sample of 10 clinicians KOLs (9 oncologists and 1 urologist) participated in the advisory board.

A detailed overview of the model structure, data and assumptions used in the company submission was presented to the participants. The rationale for extrapolating clinical trial endpoints like OS and MFS beyond the trial follow-up and the range of methods employed were carefully explained to the participants from both a practical and theoretical perspective. The six survival curve extrapolation models used in the company submission (i.e. Gompertz, Weibull, Exponential, Log-normal, Log-logistic, and Generalised Gamma) were presented alongside the trial data in a series of graphs, for each arm individually and combined and on top of the trial data. Additionally, the predicted survival (in %) for each extrapolation model at specific timepoints, i.e. 5 years, 10 years, and 15 years, was presented in tables. All data and outputs were carefully explained and all participants comprehended what the predictions would entail from a clinical practice point of view.

The participants were asked to elicit their preference for the survival distribution that they considered would best capture what is currently observed in current clinical practice for the ADT arm based on their own clinical experience and what they

believe would be plausible estimates if darolutamide were to be recommended for use in the nmCRPC setting.

All the advisors agreed that the Weibull distribution fitted most closely with the ARAMIS OS data and that the survival estimates of the Weibull model were in line with clinical expectations for the ADT alone and darolutamide treatment arms.

B2. Document B, section B.3.3, page 112. It is stated in the submission that the predicted metastasis free survival using the Weibull distribution is in line with the efficacy of ADT in clinical practice ("In the validation advisory board clinical experts agreed that the Weibull is the most plausible and conservative distribution for both arms and in line with what is currently observed in clinical practice in relation to the ADT arm"). Please provide evidence to support this assertion.

Please see response to question B1 above for details of the clinical advisory board at which the survival extrapolations were validated.

All participants agreed that the Weibull distribution fitted most closely with the MFS data from ARAMIS and that the survival estimates of the Weibull model for androgen deprivation therapy (ADT) alone seemed accurate and in line with what they would generally expect in clinical practice. Although the advisors did not have much clinical experience with darolutamide, they agreed that the survival estimates for the darolutamide arm determined by the Weibull model seemed the most plausible in the long term, and most closely aligned with the ARAMIS trial outcomes, and with their clinical experience of other novel androgen receptor therapies in patients with nmCRPC, in the short term. One advisor noted that a 5% 5-year MFS rate for the ADT alone arm may be slightly high, but this is likely to be conservative.

B3. Document B, Figures 16, 17, 20, 21, and 23. These figures are useful for showing the alternative extrapolations for overall survival, metastasis free survival and time on treatment. Please also provide tables showing the predicted proportions surviving for each outcome at selected timepoints: 5, 10, 15, 20 and 25 years.

Please see Tables 3-9 below for an overview of the survival estimates at the timepoints requested for the survival analyses performed on the 03 SEP 2018 data-

cut in the original submission as well as the more mature 15 NOV 2019 final data-cut utilised in the updated version of the cost-effectiveness model. These figures mirror the extrapolations of overall survival, metastasis free survival and time on treatment presented in Document B, Figures 16, 17, 20, 21 and 23, as well as the extrapolation models fitted to the new data-cut for overall survival and time on treatment as detailed in Appendix N.

Table 3: Survival analysis estimates MFS-BMC 03 SEP 2018 data-cut

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%**

Table 4: Survival analysis estimates OS 03 SEP 2018 data-cut

Parametric model	**Predicted survival**				
	5 years	**10 years**	**15 years**	**20 years**	**25 years**
Darolutamide + ADT arm					
Exponential	78.2%	61.1%	47.6%	37.2%	29.1%
Generalised gamma	64.7%	15.8%	0.2%	0.0%	0.0%
Gompertz	55.1%	0.1%	0.0%	0.0%	0.0%
Log-logistic	69.5%	43.7%	29.1%	20.8%	15.7%
Log-normal	75.1%	58.1%	46.9%	39.3%	33.6%
Weibull	**67.4%**	**32.6%**	**12.5%**	**4.1%**	**1.1%**

Parametric model	Predicted survival				
	5 years	10 years	15 years	20 years	25 years
ADT arm					
Exponential	70.9%	50.3%	35.5%	25.2%	17.9%
Generalised gamma	52.2%	18.8%	6.5%	2.3%	0.8%
Gompertz	25.1%	0.0%	0.0%	0.0%	0.0%
Log-logistic	50.5%	20.2%	10.0%	5.9%	3.8%
Log-normal	58.7%	33.0%	20.4%	13.5%	9.5%
Weibull	**45.0%**	**5.2%**	**0.2%**	**0.0%**	**0.0%**

Table 5: Survival analysis estimates OS 15 NOV 2019 data-cut (unadjusted for cross-over)

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%**

Table 6: Survival analysis estimates OS 15 NOV 2019 data-cut (RPSFT cross-over adjustment)

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%

Parametric model	Predicted survival				
	5 years	10 years	15 years	20 years	25 years
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	68.4%	46.8%	31.9%	21.8%	14.9%
Generalised gamma	54.3%	21.7%	8.4%	3.4%	1.4%
Gompertz	32.9%	0.0%	0.0%	0.0%	0.0%
Log-logistic	52.8%	22.5%	11.5%	6.9%	4.6%
Log-normal	59.3%	33.8%	21.0%	14.1%	9.9%
Weibull	**48.2%**	**7.5%**	**0.4%**	**0.0%**	**0.0%**

Table 7: Survival analysis estimates OS 15 NOV 2019 data-cut (IPE cross-over adjustment)

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	64.3%	41.3%	26.4%	16.9%	10.9%
Generalised gamma	49.2%	12.1%	2.2%	0.3%	0.0%
Gompertz	38.8%	0.0%	0.0%	0.0%	0.0%
Log-logistic	50.7%	20.3%	10.0%	5.9%	3.8%
Log-normal	55.8%	29.0%	16.7%	10.5%	7.0%
Weibull	**46.9%**	**6.5%**	**0.3%**	**0.0%**	**0.0%**

Table 8: Survival analysis estimates TOT 03 SEP 2018 data-cut

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 9: Survival analysis estimates TOT 15 NOV 2019 data-cut

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]

In the new November 2019 data-cut the Weibull model was the overall best fitting model for overall survival, which is consistent with the September 2018 data-cut. This shows a decrease of overall survival in the darolutamide arm compared to the older data-cut, whereas in the ADT arm an increase in overall survival is predicted. Survival estimates for time on treatment in the new data-cut go down due to the longer follow-up which means fewer patients with censored discontinuation dates.

B4. PRIORITY. For scenarios that equalise the mortality risk from a defined timepoint, it may not be appropriate to equalise this to mortality in the darolutamide arm. To explore the uncertainty around the assumed ongoing survival benefit in the model, please provide the following additional sensitivity analyses, which equalise the mortality risk in the darolutamide arm to the mortality risk in the ADT arm:

a. **After trial follow-up**

b. **After 5 years**

c. **After 7 years**

In our approach, the uncertainty around the assumed ongoing survival benefit in the model was tested where the ADT mortality risk was assumed to be the same as the mortality risk on the darolutamide arm. This approach was used given that it provided a modelled 4-year survival rate of 66% in the ADT arm, which closely aligned with the estimated 4-year survival rate in the placebo arms in the PROSPER[3] and SPARTAN[4] trials of 65%. When the ERG approach is used, the 4-year survival rate is 59% which is not so closely aligned with the survival estimate in PROSPER and SPARTAN.

The requested amendment has been made in sheets “PF_Daro” and “PF_ADT” Columns Q-W in the cost-effectiveness model (version 2.0). The switch for this scenario has been added in cell I101 in the “Control” sheet. Given that the updated November 2019 data-cut trial follow-up is ~5 years, when using the November 2019 efficacy data, only the 5 and 7 years scenarios are presented.

As presented in Table 10, using the ERG suggested approach where the mortality risk in the darolutamide arm is equal to the mortality risk in the ADT arm resulted in a significant increase in the ICERs. However, when considering the 2019 data-cut and using the ERG approach, this resulted in a significant decrease in the ICER. This is due to the 2019 ToT data estimating lower darolutamide costs, resulting in smaller incremental costs. Then, when darolutamide OS is reduced using the ERG approach, this lowers the time spent in the costly metastatic progressed health state. This further reduction in incremental costs caused by this decrease in metastatic

progressed LYs is proportionally greater than the decrease in QALYs, and therefore, the ICER lowers when list prices are assumed for subsequent therapies.

Table 10: Results of mortality risk scenario analysis

ARAMIS trial data-cut used	**Scenario**	**ICER (£/QALY): darolutamide +ADT versus ADT**	
		Company approach	**ERG approach**
September 2018	Submitted company model base case	£11,455	£11,455
	Submitted company model – 3.8 years	£15,862	£19,507
	Submitted company model – 5 years	£13,631	£16,375
	Submitted company model – 7 years	£12,182	£13,937
	Updated company model base case	**£11,270**	**£11,270**
	Updated company model – 3.8 years	£14,594	£15,488
	Updated company model – 5 years	£12,780	£13,682
	Updated company model – 7 years	£11,753	£12,433
November 2019 (unadjusted OS and ToT)	Submitted company model base case	£6,296	£6,296
	Submitted company model – 5 years	£5,015	£4,141
	Submitted company model – case – 7 years	£5,797	£5,203
	Updated company model base case	**£4,919**	**£4,919**
	Updated company model – 5 years	£983	Darolutamide dominant
	Updated company model – case – 7 years	£3,486	£1,554

Key: mCRPC, metastatic castration resistant prostate cancer; ICER, incremental cost-effectiveness ratio; OS, overall survival; ToT, time on treatment; ADT, androgen deprivation therapy.

Utility values

B5. Document B, Table 28, page 121. This table provides the estimated effect of metastasis (baseline metastases censored at day 0) on health state utility. Please provide the mean time between first documented metastasis and the EQ-5D responses that inform this utility decrement.

The EQ-5D questionnaires were collected at screening, Visit 1, Visit 4 and at the end of study treatment visit. Visit 4 occurred 16 weeks (±7 days) from the start of the study. The maximum estimated duration of the ARAMIS trial for an individual patient was 72 months. The available QoL data from the EQ-5D-3L collection is limited to early in the trial period, so there are few records for patients who have confirmed metastases. While utility values after confirmed metastases can be estimated, these are based on few records.

Table 25 of Document B from the company submission and Table 11 below show that a total of 2,687 records (1,752 darolutamide records and 935 placebo records) from 1,478 patients (941 patients receiving darolutamide and 537 patients receiving placebo) were available before metastasis was confirmed. Only 168 records (63 darolutamide records and 105 placebo records) from 144 patients (58 patients receiving darolutamide and 86 patients receiving placebo) were available after metastasis was confirmed.

In Table 11, the time from each EQ-5D record to confirmed metastases is summarised. The time from EQ-5D record to confirmed metastasis is defined as: MFS date – EQ-5D record date + 1. Therefore, a positive value denotes the number of days before metastases, while a negative value denotes the number of days after metastases**.**

Table 11: Summary of the number of observations in each visit for the EQ-5D questionnaire

Summary variables	**Number of observations** **Number of patients** **Mean time between metastasis and EQ-5D records (SD) [Days]** **Median time between metastasis and EQ-5D records (Range) [Days]**		
	Darolutamide N=955	Placebo N=554	All N=1,509
All	1,933 943 [redacted]	1,188 550 [redacted]	3,121 1,493 [redacted]
Visit			
Screening	24 24 [redacted]	14 14 [redacted]	38 38 [redacted]
Visit 1	927 927 [redacted]	544 544 [redacted]	1471 1471 [redacted]
Visit 4	876 876 [redacted]	494 494 [redacted]	1370 1370 [redacted]
End of study treatment	106 106 [redacted]	136 136 [redacted]	242 242 [redacted]
Health state (BMC)			
Before metastasis	1,752 941 [redacted]	935 537 [redacted]	2,687 1,478 [redacted]
After metastasis	63 58 [redacted]	105 86 [redacted]	168 144 [redacted]

Key: BMC, Baseline metastasis censored; SD, standard deviation.

B6. PRIORITY. Document B, Table 33, pages 133-134. A weighted average utility value for the metastatic progressed health state of 0.704 is used in the model. Please provide the rationale for applying equal post progression survival utility for both arms of the model given each arm has a different subsequent treatment distribution - with more efficacious treatments available following progression on ADT alone (such as enzalutamide and abiraterone) patients may remain in the mCRPC 1 state for longer than patients who progress on darolutamide.

As the EQ-5D-3L collection in ARAMIS was limited to the initial stages of the trial, it was not possible to use trial-based robust post-progression utility values due to the small number of observations for patients who had confirmed metastases. As such, given the paucity of evidence to support subsequent treatment-specific utilities, an assumption was made in line with TA580 to apply an estimated weighted post-progression utility to both arms. However, as we recognize the limitations of this approach, we have explored an additional option where we estimate mCRPC utility separately for the darolutamide + ADT and ADT arms, taking into consideration the proportion of patients receiving enzalutamide and abiraterone in the mCRPC 1 state. Similarly to the company submitted base case approach, the proportions of time spent in each line of therapy in the metastatic disease state (mCRPC 1, mCRPC 2, mCRPC 3 and BSC) for patients receiving enzalutamide and abiraterone in the mCRPC 1 state were sourced from TA377[5], as it was deemed the most relevant publicly available information given that disaggregated life years results were redacted in TA580.[3, 6] The mCRPC weighted average utility for each arm is estimated using the proportion of patients that received enzalutamide and abiraterone in the mCRPC 1 state with utility for patients receiving other therapies assumed to incur the same utility as the BSC arm. Detailed calculations are presented in (Table 12, Table 13 and Table 14). The estimated weighted utility of 0.743 and 0.705 is close to the clinical experts' estimates of utility in this health state (an expected range of 0.6–0.7).[2] The use of these utilities has been implemented in the model (version 2.0) in cell I96 and I98 in the "Control" sheet, Cells D10-E11 and C82-G96 in the "Utilities" sheet.

Table 12: mCRPC weighted average utility- BSC arm

	mCRPC 1	mCRPC 2	mCRPC 3	mCRPC BSC (palliative care)
Mean LYs*[5]	0.601	0.586	0.438	0.988
Utility **[3]	0.81	0.80	0.688	0.59
Average weighted utility	0.704			
Utility source[3]	EQ-5D data in PROSPER		Originally sourced from AFFIRM (TA316)	Originally sourced from the PREVAIL

Key: BSC, best supportive care; LYs, life years; mCRPC, metastatic castration resistant prostate cancer; TA, technology appraisal; BSC, best supportive care.
*sourced from TA377[5] Table B83 in the company submission.
**sourced from TA580[3] and SMC2195 DAD

Table 13: mCRPC weighted average utility- Enzalutamide arm

	mCRPC 1	mCRPC 2	mCRPC 3	mCRPC BSC (palliative care)
Mean LYs*[5]	1.923	0.324	0.000	0.818
Utility **[3]	0.81	0.80	0.688	0.590
Average weighted utility	0.750			
Utility source[3]	EQ-5D data in PROSPER		Originally sourced from AFFIRM (TA316)	Originally sourced from the PREVAIL

Key: BSC, best supportive care; LYs, life years; mCRPC, metastatic castration resistant prostate cancer; TA, technology appraisal; BSC, best supportive care.
*sourced from TA377[5] Table B81 in the company submission.
**sourced from TA580[3] and SMC2195 DAD

Table 14: mCRPC weighted average utility- Abiraterone arm

	mCRPC 1	mCRPC 2	mCRPC 3	mCRPC BSC (palliative care)
Mean LYs*[5]	1.782	0.309	0.000	0.769
Utility **[3]	0.81	0.80	0.688	0.590
Average weighted utility	0.750			
Utility source[3]	EQ-5D data in PROSPER		Originally sourced from AFFIRM (TA316)	Originally sourced from the PREVAIL

Key: BSC, best supportive care; LYs, life years; mCRPC, metastatic castration resistant prostate cancer; TA, technology appraisal; BSC, best supportive care.
*sourced from TA377[5] Table B82 in the company submission.
**sourced from TA580[3] and SMC2195 DAD

Table 15 presents the weighted average mCRPC utility for each subsequent treatment distributions source. It is important to note that in the scenario where subsequent treatment distributions are sourced from the ARAMIS trial using the “All lines” approach, the weighted average mCRPC utility is calculated using the first line subsequent treatment distribution as they are representative of the mCRPC 1 health state.

Table 15: mCRPC weighted average utility per treatment arm for each alternative subsequent treatment distribtuions in the cost-effectiveness model

Subsequent treatment distribution sources	Weighted mCRPC utility- ADT arm (SE)	Weighted mCRPC utility- darolutamide + ADT arm (SE)
UK advisory board	0.743 (0.074)	0.705 (0.070)
NICE TA580 - CDF	0.750 (0.075)	0.750 (0.075)
NICE TA580 - ERG	0.704 (0.070)	0.750 (0.075)
NICE TA580 - average (CDF & ERG)	0.727 (0.073)	0.750 (0.075)
ARAMIS - all lines	0.717 (0.072)	0.718 (0.072)
ARAMIS - first line	0.717 (0.072)	0.718 (0.072)

Key: mCRPC, metastatic castration resistant prostate cancer; ICER, incremental cost-effectiveness ratio; OS, overall survival; ToT, time on treatment; ADT, androgen deprivation therapy.

The results of this scenario using the advisory board subsequent treatment distributions are presented in Table 16 using the company submitted base case and the company updated base case with November 2019 data-cut and September 2018 efficacy data. When applying metastatic progressed utilities dependent on subsequent treatment use, the ICER moderately increased compared to the base case.

Table 16: Results of treatment-dependent post-progression utility scenario analysis

ARAMIS trial data-cut used	Scenario	ICER (£/QALY): darolutamide +ADT versus ADT
September 2018	Submitted company model base case	£11,455

ARAMIS trial data-cut used	Scenario	ICER (£/QALY): darolutamide +ADT versus ADT
	Submitted company model -different mCRPC utility per treatment arm	£12,059
	Updated company model base case (different mCRPC utility per treatment arm)	**£11,270**
	Updated company model – same mCPRC utility for both treatment arm	£10,696
November 2019 (unadjusted OS and ToT)	Submitted company model base case	£6,296
	Submitted company- different mCRPC utility per treatment arm	£6,841
	Updated company model base case (different mCRPC utility per treatment arm)	**£4,919**
	Updated company model – same mCPRC utility for both treatment arm	£4,527
Key: mCRPC, metastatic castration resistant prostate cancer; ICER, incremental cost-effectiveness ratio; OS, overall survival; ToT, time on treatment; ADT, androgen deprivation therapy.		

Subsequent treatments

B7. PRIORITY. Please comment on the likely impact on overall survival of the differences between the ARAMIS trial and current practice relating to subsequent treatment use. In particular, the proportions of patients who received enzalutamide and abiraterone in each arm.

Given the relative short follow-up of the ARAMIS trial compared with the expected long-term mCRPC health state, the subsequent treatments observed in the ARAMIS trial may not accurately represent the subsequent treatments used to manage mCRPC in UK clinical practice, especially in later lines. Therefore, subsequent treatments for mCRPC were based on the clinical experts' opinion gained at the UK validation meeting. When comparing the proportion of patients receiving each treatment in the ARAMIS trial to the percentage of patients that we would expect to see receiving each treatment in UK clinical practice, there are differences, especially between the percentages of patients that receive (or are expected to receive) enzalutamide and abiraterone upon progression on the darolutamide + ADT arm (Table 17).

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

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[2]	
	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						

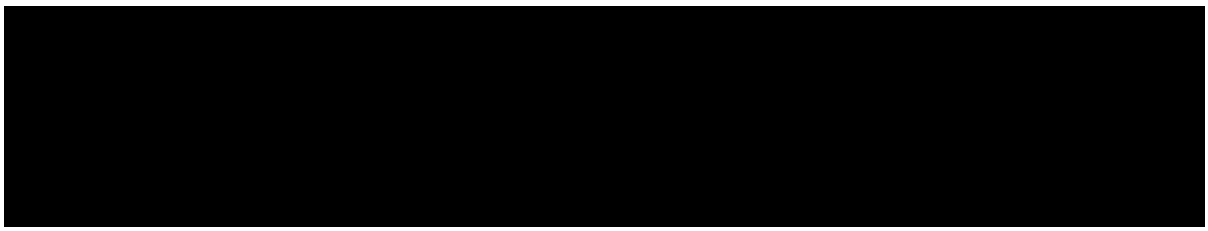
To investigate the likely impact of this on the results of the cost-effectiveness model, we conducted exploratory analyses on overall survival and subsequent therapies used in ARAMIS. Due to the greater follow-up of survival on subsequent therapy and subsequent therapy itself, the latest data cut (November 2019) was used. Figure 5 shows the KM data for the survival from subsequent treatment start date of patients that received enzalutamide, abiraterone and docetaxel in the mCRPC 1 state upon progression on the darolutamide + ADT arm. Overall survival was defined as date of death or censor minus start date of subsequent treatment + 1. The curves and confidence intervals of the three curves largely overlap and cross until month 32, and as such there is not enough evidence to suggest that the survival among patients on darolutamide + ADT is different whilst receiving abiraterone, enzalutamide or docetaxel as subsequent treatments. Similarly, Figure 6 shows the survival from subsequent treatment start date for patients on the ADT arm that received abiraterone, enzalutamide or docetaxel upon progression. The abiraterone and docetaxel curves and confidence intervals cross throughout the plot. For the enzalutamide curve however, the confidence intervals overlap with the docetaxel and abiraterone curves until approximately week 24, after which the enzalutamide curve depicts an extended plateau with a large number of censor points. Although this is not enough evidence to state that the survival among patients who have progressed

on ADT alone is different whilst receiving abiraterone, enzalutamide or docetaxel as subsequent treatments, these data suggest that subsequent enzalutamide may be more beneficial to patients who have progressed on ADT alone.

It is important to highlight the main limitations of these analyses: randomization has been broken and there are a low number of patients when stratifying by subsequent treatment received. Additionally, it is important to emphasize that the data from the ARAMIS trial was not powered to detect the difference in any subsequent treatment effects.

Figure 5: Kaplan-Meier plot of overall survival of the darolutamide + 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)

Figure 6: 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)



Key: OS, overall survival.

In summary, we cannot categorically conclude that the survival for patients in the ARAMIS trial is affected by the subsequent treatment received in the mCRPC 1 state on either treatment arm based on the results from the presented exploratory analyses. As such, it is difficult to conclude whether the overall survival estimates in the economic model are biased by the difference in proportions of abiraterone, enzalutamide and docetaxel between the UK clinical practice and the ARAMIS trial.

Should subsequent treatment with abiraterone or enzalutamide after ADT lead to a greater survival than subsequent treatment with other therapies such as docetaxel, the overall survival estimate for ADT in the economic model may be slightly less than expected. Although we are aware that methodologies exist that could correct overall survival for differences in expected and observed subsequent treatment use (such as those presented in TA377[5] [IPCW and two stage method] to correct for subsequent treatments not available in the UK), these adjustment methods come with the inherent uncertainties. First, it is not clear how one would combine the cross-over adjustment for switching from control to intervention with adjustment for non-UK standard subsequent treatment use, as these are not mutually exclusive given that some patients could have both events in a sequence. Second, it may require pooling treatments to make this viable with the low number of patients upon stratification, and as such this would result in further challenges regarding the assumption of a pooled treatment, which would introduce further uncertainties into the long-term treatment effect.

Because the current model base case displays a disconnect between the survival data used and the costs incurred regarding subsequent treatments, we presented a scenario analysis in the company submission Document B Section B.3.8, where it was shown to have a moderate impact on the ICER. Due to the changes in the base case as described in A3, we have presented the updated scenarios again in Table 18. In all of these scenarios, the ICER is below the willingness to pay threshold of £30,000.

Table 18: Results of subsequent treatment distribution based on the ARAMIS trial scenario analysis

ARAMIS trial data-cut used	**Scenario**	**ICER (£/QALY): darolutamide +ADT versus ADT**
September 2018	Submitted company model base case	£11,455
	Submitted company model – ARAMIS first line	£25,377
	Submitted company model – ARAMIS all lines	£25,797
	Updated company model base case	**£11,270**
	Updated company model base case – ARAMIS first line	£25,773
	Updated company model base case – ARAMIS all lines	£26,274
November 2019 (unadjusted OS and ToT)	Submitted company model base case	£6,296
	Submitted company model - ARAMIS first line	£26,206
	Submitted company model – ARAMIS all lines	£26,782
	Updated company model base case	**£4,919**
	Updated company model base case – ARAMIS first line	£26,277
	Updated company model base case – ARAMIS all lines	£26,969

Key: mCRPC, metastatic castration resistant prostate cancer; ICER, incremental cost-effectiveness ratio; OS, overall survival; ToT, time on treatment; ADT, androgen deprivation therapy.

B8. Document B, Table 43, pages 152-153.

- **Please clarify where the Cancer Drugs Fund treatment distribution that feeds into the scenario analysis comes from; i.e please provide a page or table reference in the committee papers from TA580. It is not**

currently possible to identify these data in reference 75 [meeting papers for the first NICE committee meeting discussion of enzalutamide for non-metastatic hormone-relapsed prostate cancer TA580]).

- **Please clarify the data used for the assumption on use of enzalutamide after progression to having metastatic disease on darolutamide**

The Cancer Drugs Fund subsequent treatment distribution was explored in one of the scenario analyses in our original submission and assumes patients would be receiving subsequent enzalutamide and abiraterone treatment following progression to metastatic disease on darolutamide. This distribution was discussed at the Appraisal Committee Meeting for TA580 and was included as academic in confidence in our original submission for completeness reasons only. We believe this distribution does not accurately reflect clinical practice in the UK, as informed by an advisory board of 10 leading UK clinicians, and is not in line with current NHS England policy in relation to new generation androgen receptor antagonists.[2]

B9. Document B, page 117. For both the ADT and darolutamide + ADT model arms, background ADT is applied for the entire model horizon. The submission states that this assumption was validated by clinical experts. Please clarify if the clinical experts consulted were unanimous with respect to their advice on this assumption.

At the clinical advisory board organised by Bayer on the 4th of February 2020, a group of 10 leading UK clinicians (9 oncologists and 1 urologist) were split into two groups and were asked to inform the subsequent treatment distribution of patients progressing to mCRPC based on their current clinical practice experience and how this distribution would change if darolutamide is recommended for use in nmCRPC.[2] Each group suggested that background ADT will be given to all patients throughout the mCRPC state. Participants also suggested that background ADT is provided in nmCRPC state.

Costs

B10. Document B, Table 47, page 164. The model uses PSSRU 2019 costs rather than NHS reference costs for the unit cost of an outpatient consultant visit and for seeing a band 4 nurse. Please justify the following:

i. The PSSRU costs are for an hour of staff time. Please explain the rationale behind the use of 1 hour of a band 4 hospital nurse's time for the administration of ADT treatment.

There is a lack of consistency in prior prostate cancer NICE appraisals with regards to costing the administration of subcutaneous therapies, ranging from no costs in TA580[6], to costing admin based on the average of 15 minutes of a practice nurse visit and 15 minutes of day ward nurse time in TA404.[7] In the absence of an established costing method, 1 hour of a band 4 hospital nurse time was assumed for our model. However, in order to explore how sensitive the model is to this input, we have conducted a further scenario analysis where we have used the administration costs from TA404, (inflated to 2019) of £12.99. The switch for this scenario has been added in cell I110 in the "Control" sheet. This scenario marginally decreases the ICER (Table 19).

Table 19: Results of alternative subcutaneous injection administration costs scenario analysis

ARAMIS trial data-cut used	Scenario	ICER (£/QALY): darolutamide +ADT versus ADT
September 2018	Submitted company model base case	£11,455
	Submitted company model – TA404 approach	£11,281
	Updated company model base case	**£11,270**
	Updated company model base case – TA404 approach	£11,042
November 2019 (unadjusted OS and ToT)	Submitted company model base case	£6,296
	Submitted company model – TA404 approach	£6,071
	Updated company model base case	**£4,919**
	Updated company model base case – TA404 approach	£4,695

Key: mCRPC, metastatic castration resistant prostate cancer; ICER, incremental cost-effectiveness ratio; OS, overall survival; ToT, time on treatment; ADT, androgen deprivation therapy.

ii. Please justify why the NHS reference cost were not used for outpatient consultant appointments. For example, there is a non-admitted consultant led medical oncology detailed in the reference costs (service code 370).

As detailed in the company's submission Document B Section B.3.5, the resource use costs utilized to cost the outpatient consultant appointment was sourced from the latest PSSRU 2019 costs using an hour cost for a hospital doctor. This approach is line with TA580[6] and TA377[5] where PSSRU costs was used to source the outpatient consultant cost. However, to investigate the model sensitivity to the submitted company approach, we have implemented a scenario where the non-admitted consultant led medical oncology cost of £194.17 sourced from the NHS reference cost 2018/2019 (CL Non-Admitted Face-to-Face Attendance, Follow-up code 370) is used. The switch for this scenario has been added in cell I112 in the "Control" sheet. This scenario moderately increases the ICERs (Table 20).

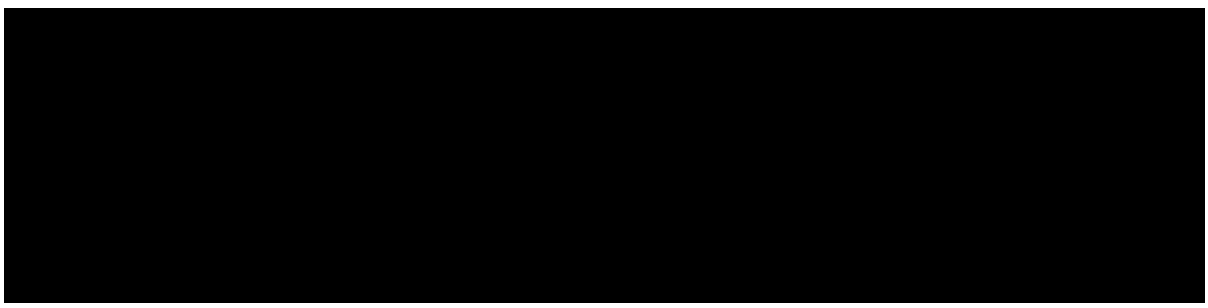
Table 20: Results of alternative consultant led resource use costs scenario analysis

ARAMIS trial data-cut used	**Scenario**	**ICER (£/QALY): darolutamide +ADT versus ADT**
September 2018	Submitted company model base case	£11,455
	Submitted company model – NHS reference cost approach	£11,999
	Updated company model base case	**£11,270**
	Updated company model base case – NHS reference cost approach	£11,855
November 2019 (unadjusted OS and ToT)	Submitted company model base case	£6,296
	Submitted company model – NHS reference cost approach	£6,746
	Updated company model base case	**£4,919**
	Updated company model base case – NHS reference cost approach	£5,410
Key: mCRPC, metastatic castration resistant prostate cancer; ICER, incremental cost-effectiveness ratio; OS, overall survival; ToT, time on treatment; ADT, androgen deprivation therapy.		

B11. An adjustment is made to subsequent treatment costs in the model ('Subseq-Trt', cells G10:I12), to account for the expected proportion of patients making the transition to each subsequent line of therapy in each treatment arm. Please clarify why you chose this approach rather than explicitly modelling transition through mCRPC sub-states based on treatment durations and cycle specific probabilities of death.

Although we fully recognize the limitations of the current model structure, it is important to highlight the inherent uncertainties when the mCPRC sub-states are explicitly modelled. As discussed in the company's submission, such an approach would introduce significant uncertainties to the cost-effectiveness model given that data to estimate transitions through mCRPC sub-states is not available in ARAMIS and would be based on external data/assumptions. This was further supported by the clinical experts'[2] where they agreed that the current model structure is appropriate given the availability of trial and publicly accessible data. This is also in line with the committee and Evidence Review Group's (ERG) opinion in TA580,[6] where they expressed concerns about the proposed sequence and transition estimates between the progressed states of the company's model. However, to overcome the limitation of the submitted model structure as part of this appraisal, the proportion of patients and time of experiencing a first, secondary and tertiary progression was estimated from the model using the extrapolated ARAMIS OS and MFS data. In addition, as illustrated in Figure 7, using the Weibull distribution to model OS assumes an increasing probability of death as patients progress through the model health states. The costs and utility associated with each subsequent treatment line is accounted for within the mCRPC health states. This is further discussed in the company's submission Sections B.3.4 and B.3.5.

Figure 7: The per cycle estimated mortality for patients on the darolutamide +ADT and ADT arms when using the Weibull distribution versus general population mortality



Key: ADT; androgen deprivation therapy

In response to the queries in the ERG clarification call, we have estimated the occupancy in each of the metastatic disease sub-states assumed as part of this model structure. The mean LYs for each of the progressed disease health states was estimated using the time at which patients progressed into each of the metastatic disease sub states based on the weighted average treatment duration of each line of therapy; these calculations can be found in cells B51-D57 in the "Post_submission" sheet of the model (version 2.0):

1. mCRPC 1 = Average Time of progression into mCRPC 2 – Average Time of progression into mCRPC 1
2. mCRPC 2 = Average Time of progression into mCRPC 3 – Average Time of progression into mCRPC 2
3. mCRPC 3 = Average Time of progression into BSC – Average Time of progression into mCRPC 3
4. BSC = Total undiscounted mean mCRPC Lys - Average Time of progression into BSC

The estimated mean undiscounted LYs for each of the mCRPC sub states is shown in Table 21, for the updated company base case. As expected, patients on the ADT arm stay on average an extra 0.79 years in the mCRPC 1 state compared with patients who progressed on the darolutamide + ADT arm given that approximately 75% of patients on the ADT arm receive enzalutamide or abiraterone as a

subsequent therapy in the mCRPC 1 health state and are as such expected to stay longer in that sub-state given the relatively better survival outcomes and tolerability when receiving enzalutamide and abiraterone versus docetaxel.

Table 21: Mean Lys by mCRPC sub-states

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

B12. In the model, subsequent treatment costs have been discounted - as the average discount factor applied to costs across the average subsequent treatment duration (found on Subseq Trt sheet cells G27 and K27). The average does not appear to be taken across the full subsequent treatment duration period. Please check this and further clarify the approach taken to ensure appropriate discounting of the subsequent treatment cost streams.

As stated in the company's submission Section B.3.5, given that subsequent treatments are administered for a number of cycles, discounting was applied while accounting for the greater discounting that would apply to later doses of subsequent treatments. As such, the discount rate for each patient entering the metastatic state is estimated by taking the average discount rate from the time a patient enters the metastatic disease state until the end of the subsequent treatment duration. The subsequent treatment duration was estimated by taking the weighted sum of the distribution of treatments at each line of therapy and their average duration. However, in response to this question, we have explored two alternative simpler discounting approaches.

In the first alternative approach, the estimated one-off acquisition and administration costs of each subsequent treatment were discounted based on their median duration (refer to cells H91:I98 on the "Subseq_Trt" sheet). Then, the pooled one-off estimates for all subsequent treatments in the mCRPC state are also discounted to account for the timing of initiating each line (e.g. the difference between average

time of progression to second line and time of progression to first line (refer to cells G105-H105 and G112-H112 on the “Subseq_Trt” sheet) in the cost-effectiveness model (version 2.0).

As a second alternative scenario, we have applied the models per cycle discount rate to the subsequent treatment one-off cost at each cycle. The switch for these scenarios has been added in cell I93 on the ”Control” sheet.

The results of the above mentioned scenarios are presented in Table 22. All scenarios have been run using the September 2018 and November 2019 data-cut using the submitted company base case and the updated company base case. The alternative continuous discounting scenario resulted in a slight increase in the ICER, but where the discount is applied per cycle, this resulted in moderate decrease in the ICER.

Table 22: Results of subsequent treatment discounting scenario analysis

ARAMIS trial data-cut used	**Scenario**	**ICER (£/QALY): darolutamide +ADT versus ADT**
September 2018	Submitted company model base case	£11,455
	Submitted company model -company alternative approach 1	£11,549
	Submitted company model -company alternative approach 2	£10,960
	Updated company model base case (company alternative approach 1)	**£11,270**
	Updated company model base case – company original approach	£11,144
	Updated company model – company alternative approach 2	£10,583
November 2019 (unadjusted OS and ToT)	Submitted company model base case	£6,296
	Submitted company model -company alternative approach 1	£6,399
	Submitted company model -company alternative approach 2	£5,552
	Updated company model base case (company alternative approach 1)	**£4,919**
	Updated company model base case – company original approach	£4,787
	Updated company model – company alternative approach 2	£3,902

ARAMIS trial data-cut used	Scenario	ICER (£/QALY): darolutamide +ADT versus ADT
Key: mCRPC, metastatic castration resistant prostate cancer; ICER, incremental cost-effectiveness ratio; OS, overall survival; ToT, time on treatment; ADT, androgen deprivation therapy.		

B13. In the model, the discounting method used for treatment costs (e.g. sheet 'PF_Daro', cell AL12) suggests that costs are incurred at the end of the cycle rather than at the beginning. Please provide an adjustment to the model, which discounts costs as occurring at the start of each period. A patient must collect the cycle's treatment from the chemist, which is then take over the cycle. Therefore, the cost of this should be discounted using the discount factor at the start of the period.

This amendment has been made in sheets "PF_Daro" columns AM- AW and "PF_ADT" columns AK-AS in the cost-effectiveness model (version 2.0). The switch for this scenario has been added to cell I91 of the "Control" sheet.

All scenarios have been run using the September 2018 and November 2019 data-cut using the submitted company base case and the updated company base case. As shown in Table 23 this adjustment resulted in small increase in the ICER.

Table 23: Results of discount method scenario analysis

ARAMIS trial data-cut used	Scenario	ICER (£/QALY): darolutamide +ADT versus ADT
September 2018	Submitted company model base case	£11,455
	Submitted company model -ERG suggested discounting approach	£11,475
	Updated company model base case (ERG suggested discounting approach)	**£11,270**
	Updated company model – company's original discounting approach	£11,240
November 2019 (unadjusted OS and ToT)	Submitted company model base case	£6,296
	Submitted company model -ERG suggested discounting approach	£6,312

ARAMIS trial data-cut used	Scenario	ICER (£/QALY): darolutamide +ADT versus ADT
	Updated company model base case (ERG suggested discounting approach)	**£4,919**
	Updated company model – company's original discounting approach	£4,906
Key: mCRPC, metastatic castration resistant prostate cancer; ICER, incremental cost-effectiveness ratio; OS, overall survival; ToT, time on treatment; ADT, androgen deprivation therapy.		

B14. Document B. Table 38 page 143. Healthcare resource use is assumed to be the same between treatment groups. Please clarify this assumption and explain why a patient undergoing darolutamide treatment would use the same amount of resources as a patient undergoing ADT treatment.

In TA580 the submitting company assumed a lower healthcare resource use in the enzalutamide + ADT arm compared to the ADT alone arm. This was criticised by the ERG which preferred using equal resource use between the treatment arms, which is the approach we have implemented in our cost-effectiveness model. The healthcare resource utilisation elements included in our submission consist of routine check-ups, tests and scans specific to patients with prostate cancer and are not expected to change with the use of darolutamide.

B15. Page 117 of document B states: "For both the ADT and Darolutamide + ADT model arms…background ADT was applied for the entire model horizon". In the model, looking at the cost calculations for the metastatic CRPC state (PF_Daro, Column AN) it appears that ADT background costs per cycle are only applied to the proportion of the cohort leaving the MFS state in each cycle. Please either provide the rationale for this or adjust the model so that it is consistent with page 117 of document B. The same issue can be extended to the PPS administration cost in column (AQ) and the corresponding columns in the PF_ADT worksheet.

We have amended the approach of applying the ADT per cycle cost in the PPS state to be in line with the approach used in the PFS state. The amendment has been made in sheets "PF_Daro" columns AO and AR and "PF_ADT" columns AL and AN

in the cost-effectiveness model (version 2.0). The switch for this scenario has been added to cell I105 of the "Control" sheet.

All scenarios have been run using the September 2018 and November 2019 data-cut using the submitted company base case and the updated company base case. As detailed in Table 24, the adjustment resulted in moderate increase in the ICER.

Table 24: Results of post-progression ADT costing method scenario analysis

ARAMIS trial data-cut used	**Scenario**	**ICER (£/QALY): darolutamide +ADT versus ADT**
September 2018	Submitted company model base case	£11,455
	Submitted company model -company update approach	£11,835
	Updated company model base case (company update approach)	**£11,270**
	Updated company model – company's original approach	£10,858
November 2019 (unadjusted OS and ToT)	Submitted company model base case	£6,296
	Submitted company model -company update approach	£6,156
	Updated company model base case (company update approach)	**£4,919**
	Updated company model – company's original approach	£5,071

Key: mCRPC, metastatic castration resistant prostate cancer; ICER, incremental cost-effectiveness ratio; OS, overall survival; ToT, time on treatment; ADT, androgen deprivation therapy.

Company reference pack

B16. Reference 3 (Bayer. Meeting Report. National Institute of Health and Care Excellence (NICE) submission for darolutamide in high-risk, non-metastatic castration-resistant prostate cancer (nmCRPC) advisory board 2020) in document B does not appear to have been included in the company reference pack. Please provide this reference.

Reference has now been provided.

References

1. Latimer N, Lambert P, Crowther M, et al. Methods for estimating survival benefits in the presence of treatment crossover: A simulation study. Available at: https://www.sheffield.ac.uk/polopoly_fs/1.228038!/file/N_Latimer_detailed.pdf. Accessed: 22 April 2020.
2. Open Health Medical Communications. Meeting Report. National Institute of Health and Care Excellence (NICE) submission for darolutamide in high-risk, non-metastatic castration-resistant prostate cancer (nmCRPC) advisory board 4 February 2020. Data on file.
3. National Institute for Health and Care Excellence (NICE). ID1359 Enzalutamide for non-metastatic hormone-relapsed prostate cancer 1st ACM. 2019. Data on File.
4. Small EJ, Saad F, Chowdhury S, et al. Apalutamide and overall survival in non-metastatic castration-resistant prostate cancer. *Ann Oncol*. 2019; 30(11):1813-20.
5. National Institute for Health and Care Excellence (NICE). TA377: Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated. 2015. Available at: https://www.nice.org.uk/guidance/TA377/documents/final-appraisal-determination-document. Accessed: 30 January 2020.
6. National Institute for Health and Care Excellence (NICE). TA580: Enzalutamide for treating non-metastatic hormone-relapsed prostate cancer. 2019. Available at: https://www.nice.org.uk/guidance/ta580. Accessed: 31 May 2019.
7. National Institute for Health and Care Excellence (NICE). TA404: Degarelix for treating advanced hormone-dependent prostate cancer. 2016. Available at: https://www.nice.org.uk/guidance/ta404. Accessed: 22 April 2020.

NICE National Institute for Health and Care Excellence

Patient organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

NICE National Institute for Health and Care Excellence

1.Your name	[redacted]
2. Name of organisation	Prostate Cancer UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Prostate Cancer UK is the UK's leading charity for men with prostate cancer and prostate problems. We support men and provide information, find answers through funding research and lead change to raise awareness and improve care. The charity is committed to ensuring the voice of people affected by prostate disease is at the heart of all we do.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	Prostate Cancer UK has a policy that funding from pharmaceutical and medical device companies will not exceed 5% of its total annual income. During the financial year 2014/2015 donations from such organisations, expressed as a percentage of our total annual income, were less than 0.1%. We have received £20,500 of funding from Bayer in the last 12 months. This funding was specifically for our improvement programme to provide clinicians with soft skills to drive improvements. We have received £65,000 of funding from Janssen, manufacturer of Apalutamide, in the last 12 months. This funding was specifically for; our project encouraging greater implementation of mpMRI to diagnose localised prostate cancer; and education. We have received £35,500 of funding from Astellas, manufacturer of Enzalutamide, in the last 12 month. This funding was specifically for our improvement programme and education for our specialist nurses. We have commented on Enzalutamide and Apalutamide appraisals in this indication.

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Desk research and our own knowledge of the experiences of men. We have spoken with our specialist nurses about their experience of speaking with men in this indication. We have also questioned leading clinicians on approaches to treatment in this indication. It is more difficult to canvass the views of patients in this specific indication, because the indication is extremely small.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Localised and locally-advanced prostate cancer are largely asymptomatic. Patients with this condition may experience lower urinary tract symptoms including poor stream and frequency. Patients with localised and locally advanced prostate cancer, whose PSA levels indicate that they are no longer castrate will very likely, if no visible metastases are identified, suffer from the anxiety of having no treatment options available. They will have to wait, receiving periodic scans, to determine whether their prostate cancer has metastasised before any further treatment options are open to them. This is because there are no other treatments licensed for non-metastatic castrate-resistant prostate cancer. This will cause particular anxiety in those patients with ‘high risk’ stages of the disease who will have an increased

likelihood of a rapidly rising PSA being an indicator of prostate cancer progression, but have nothing available to them to prevent or delay that progression.

Darolutamide will enable them to delay progression to metastatic prostate cancer which can be symptomatic and which includes the following evidence-based symptoms[i]:

- Fatigue.
- Pain, most commonly caused by prostate cancer that has spread to the bones.
- Urinary problems, this includes problems emptying the bladder, incontinence, blood in urine and kidney problems.
- Bowel problems including constipation, diarrhoea, faecal urgency, faecal incontinence, pain, bowel obstruction and flatulence.
- Broken bones, fractures caused by bone thinning.
- Sexual problems, including reduced libido and difficult getting or keeping an erection.
- Lymphoedema, primarily around the legs.
- Anaemia, caused by damage to bone marrow.
- Metastatic spinal cord compression, as cancer cells grow in or near the spine, which evidence suggests can occur in 1 to 12% of patients[ii].
- Hypercalcaemia, caused by calcium leaking from the bones into the blood.
- Eating problems

It is important to note that men are unlikely to experience all the above symptoms, as some will depend on the treatments received, while others will be the result of metastases and therefore dependent on their location. The severity of symptoms will also differ among men, while the likelihood of some of the most severe symptoms, for example Lymphoedema can be rare and vary between 1-20%[iii].

For some men, living with metastatic prostate cancer can be hard to deal with emotionally, especially as there are no current curative treatments for this stage of the disease. Symptoms and treatments can be draining and make men feel unwell.

The pressure of advanced cancer can also put a strain on relationships. Metastatic prostate cancer and its treatments might mean that partners or family need to do more for patients, such as running the home or

	caring responsibilities. Additionally, the symptoms of metastatic prostate cancer and the side effects of treatments can make it difficult to work. a partner providing care might not be able to work as much either. Everyday tasks may become more difficult and respite care may be required to give carers a break. As the disease progresses, more palliative care and treatments will be offered. This includes palliative radiotherapy to ease bone pain, blood in urine and swollen lymph nodes Men and their carers will benefit from the opportunity for an average 22 months delay of progression to metastatic prostate cancer and its potential to impact negatively on their quality life.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Currently, men who are castrate resistant but with no visible metastases have no treatment options. They must wait for their cancer to metastasise, receiving periodic tests to diagnose metastases, before treatment options become available to them. It is possible that the men in this indication already have advanced prostate cancer, but current imaging techniques, like bone and CT scans are limited in their ability to identify metastases. More advanced imaging modalities may reduce the size of the non-metastatic castrate resistant patient population because of their increased accuracy in the detection of metastases. These include PET-CT and whole-body MRI which are not currently available at initial diagnosis. There is increasing use of PET-CT for patients experiencing recurrence after treatment for localised prostate cancer. These men will have exhausted or ruled out radical treatment options including radical prostatectomy, and brachytherapy. These men and their carers will experience anxiety at the lack of treatment options, particularly if the man's PSA is rising rapidly.
8. Is there an unmet need for patients with this condition?	Yes, once radical treatment options have been exhausted or ruled out and the man has become castrate-resistant, there are no further treatment options for men until the prostate cancer metastasises elsewhere in the body. Patients are left in limbo, periodically receiving imaging to determine whether the cancer has metastasised. Once the cancer progresses, treatment options for castrate-resistant metastatic prostate cancer will be available to these patients. These only provide an average of 4 months additional survival.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The ARAMIS trial has found that Daralutamide delays the progression of prostate cancer by an average of 22 months, enabling patients to postpone symptomatic events that occur once prostate cancer has metastasised. This treatment gives patients the ability to actively treat their condition rather than to just wait for their cancer to progress. It can delay the time that the patient can live without the symptoms and side-effects associated with advanced prostate cancer. For men with chronic comorbidities this treatment has the potential to delay prostate cancer progression to the point of non-cancer specific mortality. Some common adverse effects, such as fatigue and asthenia, were less common than see in trials with comparator next generation androgen-receptor inhibitors (Enzalutamide and Apalutamide). Furthermore,, Darolutamide was not associated with higher incidence of falls or fractures than placebo (as seen in other comparator next-generation androgen-receptor inhibitors). This meant that there was less discontinuation of the drug due to adverse side effects, including among a patient cohort with a previous history of seizures.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	According to the ARAMIS trial, the incidence of side effects between those receiving Darolutamide and those receiving the placebo was generally similar, with the exception of fatigue. Incidence of dizziness, rash, hypertension and cognitive disorder showed a slight difference between the Darolutamide and placebo groups. For patients with locally advanced disease it is asymptomatic so patients may be reluctant to move from a state where they have no symptoms or side-effects to one where they take treatment and experience side-effects.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	As the clinical trial for Darolutamide (ARAMIS) demonstrates and the licence will likely reflect, this treatment will be more effective in patients classified as having 'high risk' non-metastatic castrate-resistant prostate cancer. High risk is defined as a prostate-specific antigen doubling time of 10 months or less during continuous androgen-deprivation therapy. Further analysis of the data from the ARAMIS trial may find stratified patient groups are more or less likely to benefit from the treatment. Patients in the ARAMIS trial were stratified according to PSA doubling time (>6 months vs. <6 months).
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**No**

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Patients with metastatic castrate-resistant prostate cancer currently have no treatment options available to them This constitutes an unmet need.
- It is possible that patients in this indication have advanced prostate cancer, but some current imaging techniques are limited in their ability to identify metastases.

- The lack of treatment options can cause great anxiety to men and then carers, who have evidence of a likelihood of cancer progression from rising PSA levels.

- Some common adverse effects, such as fatigue and asthenia, were less common than see in trials with comparator next generation androgen-receptor inhibitors (Enzalutamide and Apalutamide). Furthermore, Darolutamide was not associated with higher incidence of falls or fractures than placebo (as seen in other comparator next-generation androgen-receptor inhibitors). This meant that there was less discontinuation of the drug due to adverse side effects, including among a patient cohort with a previous history of seizures.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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[i] References for each symptom available on request.
[ii] European Urology Volume 44 Issue 5 *Spinal Cord Compression in Metastatic Prostate Cancer* H Tazi et al. November 2003
[iii] Journal of Lymphoedoma Volume 5 Number 2 *Cancer-related lymphoedema in males: a literature review* Cosgriff & Gordon 2010

NICE National Institute for Health and Care Excellence

Patient organisation submission

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

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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	TACKLE Prostate Cancer
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Tackle is a patient centred charitable organisation whose aims are to support men and their families whose lives are affected by prostate cancer. In addition we aim to represent the opinions of patients on any subject which is relevant to the diagnosis and treatment of prostate cancer. We also support local prostate cancer support groups around the UK. We represent 91 support groups in England and Wales and through them have 15,000 members - men and their families whose lives have been affected by prostate cancer.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**NO**

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**NO**
5. How did you gather information about the experiences of patients and carers to include in your submission?	Tackle gain regular feedback from our members via face to face contact at local and national meetings, from direct contact by telephone from individuals and from the questions and queries of patients on our patient helpline. We have a medical advisory board who advise when and where necessary. I do not have personal experience of being treated with Darolutamide. The clinical indication under discussion is a potentially new indication for use of the drug and thus no patient has direct experience of using it at this point in their treatment pathway apart from those patients involved in clinical trials. However, I have spoken with patients who are faced with the clinical scenario of non-metastatic hormone-relapsed disease and fully understand their needs and concerns. Tackle believe that it is appropriate for me to speak on their behalf.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	The terms ‘non-metastatic castrate resistant prostate cancer’ and ‘non-metastatic hormone relapsed prostate cancer’ and even 'biochemical recurrence of prostate cancer' are unintelligble to the vast majority of patients. However the journey that many patients can relate to is: 1. Localised disease treated with surgery or radiotherapy

	2. A subsequent rise in PSA treated successfully with hormone therapy (Androgen Deprivation Therapy - ADT) 3. A further subsequent rise in PSA as ADT fails to work. From a patient's perspective, knowing they have a clinical situation where identifiable spread of the disease is almost inevitable, it is extremely hard for them to understand why treatment cannot be offered earlier to potentially delay (or possibly even prevent) the onset of this spread and thus potentially to increase their life span. It can be a source of considerable distress and may be of long duration until spread is positively identified. The significant psychological distress is in addition to any physical symptoms that may also be experienced by the patient at that time. The emotional trauma of knowing that there is yet another recurrence of their cancer but no treatment can currently be offered is both alien to patients and deeply distressing, and can be summed up in this comment: "*I was given treatment for my first recurrence and it worked for a long while. Why can I not have treatment now with this second episode. We all know there's something there - my PSA is rising quite fast. Why do I have to wait until it might be too late?*" Equally there can potentially be an alteration in the relationship between oncologist and patient. Some patients can become angry with their doctors at times. There are no adequate guidelines or treatments that the doctor can refer to. Feelings of despair, hopelessness and frustration are not uncommon on both sides of the fence. The patient viewpoint is best summarised by what patients have told us: "*Why am I waiting for the inevitable to happen before treatment can be started?*" "*You know something is going wrong. Why am I not having something done now?*" "*To be honest, to know my disease is worsening but not being able to know where this is happening and in addition not being able to have any treatment is unbearable. In a strange way I would feel better if you had told me I had definitely got spread - at least I would be getting some treatment now. At least I would have an end-point to relate to.*"

	No patient expects 'miracles' at this stage of disease. However, treatment that can extend life with a good quality would bring enormous benefits both physiologically and psychologically to patients and their families/carers. Families & Carers often feel very impotent in helping their relatives through their journey with cancer of any sort. This can be particularly apparent in nmHRPC where the added stress of "*knowing something is happening but not knowing where*" can be immense. Adequate therapy at this stage with treatments which produce an acceptable side effect profile would be of immense value.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Almost by definition, mHRPC will have passed through a non-metastatic phase. Around 1/3rd of patients with nnmHRPC will have progressed to identifiable mHRMPC within 2 years. There is currently no agreed treatment pathway or specific drug licensed for use in nmHRPC. ADT alone will no longer be controlling the advancing disease but no additional therapies are currently recommended. Some patients have reported having treatment with steroids and other forms of ADT (eg Bicalutamide and dexamethasone). Others (the majority) are offered nothing. Equally there are discrepancies of opinion as to when, if ever, such treatment should start. There are no such treatments currently available to these patients. They do not even have the ability to choose whether they wish to undergo further additional therapy or not. Basically their only option is to wait for the inevitable metastases to become apparent - by then it might be too late for adequate treatment. The development of bone metastases have significant consequences medically, have increased cost issues to the NHS and impact on the quality of life of the patient. This differs greatly from the situation where distant spread has been positively identifiable and treatments such as Enzalutamide and Abiraterone are approved for use.

8. Is there an unmet need for patients with this condition?	Yes. There is no definitive clarity for either patients or clinicians as to how this clinical scenario should be managed. Currently the only option to patients with nmHRPC other than just seeing their PSA rise and waiting for metastases to be found is to have a Gallium^{68} PSMA PET scan. These scans are not standard practice on the NHS but may be available in some parts of the UK either via the private sector or as part of a research project. Patients undergoing PSMA scans may well demonstrate secondary spread that would have otherwise gone un-noticed. 2 patients have spoken to me concerning this - one could afford to pay privately, the other could not. The first patient went on to have successful localised radiotherapy to 2 small metastases. The other just had to continue to wait….he described his position as "*fiscal euthanasia - you can get the right investigations and treatment if you can afford it*".
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The major impact of having earlier treatment for nmHRPC has to be the increased time before metastases become apparent, the increase in potential life-span and the significant decrease in stress to the patient. Longevity of life on its own does not always reflect the views of patients where the quality of that increased life span is equally important. Some men with nmHRPC will have symptoms but not all. Bone metastases are frequently extremely painful, produce an increased risk of bone fractures and the often com plex orthopaedic surgery that might follow from that. Increased time to progression of such adverse events has to be a significant advantage. One other positive outcome would be the ability of the treating healthcare professionals to provide adequate therapy. There are no guidelines even to how often and what special investigations/scans should be performed in this scenario and how treatment should be progressed. It is a situation un-acceptable to all concerned.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The ultimate aim for a patient is that any new/additional therapy should have the maximum benefits but with minimal additional side effects. Drugs currently available (e.g. Enzalutumide, Abiraterone) have, in the main, a better side effect profile than chemotherapies such as docetaxel and are well tolerated by many. Darolutamide would appear to have a similar or improved side effect profile to existing drugs. Taking medication by mouth is an easy and acceptable route of administration. As with other drug therapies, regular monitoring of the patient will be required, but this could potentially occur mainly in the community rather than a hospital setting. Cost of therapy may be an issue and will have an additional financial burden on healthcare providers. This, however, is not the responsibility / concern of the patient. There is always concern that provision of a treatment may not always be available on cost grounds despite a treatment being 'approved' by regulatory bodies.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	It is stated by the pharmaceutical company that, because Darolutamide crosses the blood/brain barrier poorly, then the risks of seizures is reduced. It is not within the remit of a patient representative to comment on this.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**NO**
Other issues	
13. Are there any other issues that you would like the committee to consider?	None at the moment
Key messages	

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Hormone relapsed PCa is a problem in patients where advancing disease is no longer responding to androgen deprivation therapy (ADT) / hormone therapy. There are currently no approved treatments available for this so-called 'biochemical' recurrence of PCa where PSA levels are rising but no metastases can be found on conventional scanning methods
- Patients can be extremely distressed by the situation of knowing that their cancer is advancing but no treatment can be offered.

- There appears to be little consensus as to how this clinical scenario should be managed.
- The ultimate outcome for both the patient and their families / carers is not solely the prolongation of life but also the potential production of an extended period of time during which quality of life issues - both physical and psychological - are equally important.
- This clinical scenario constitutes a huge unmet need.

Thank you for your time.

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

Produced by Aberdeen HTA Group

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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 ≥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

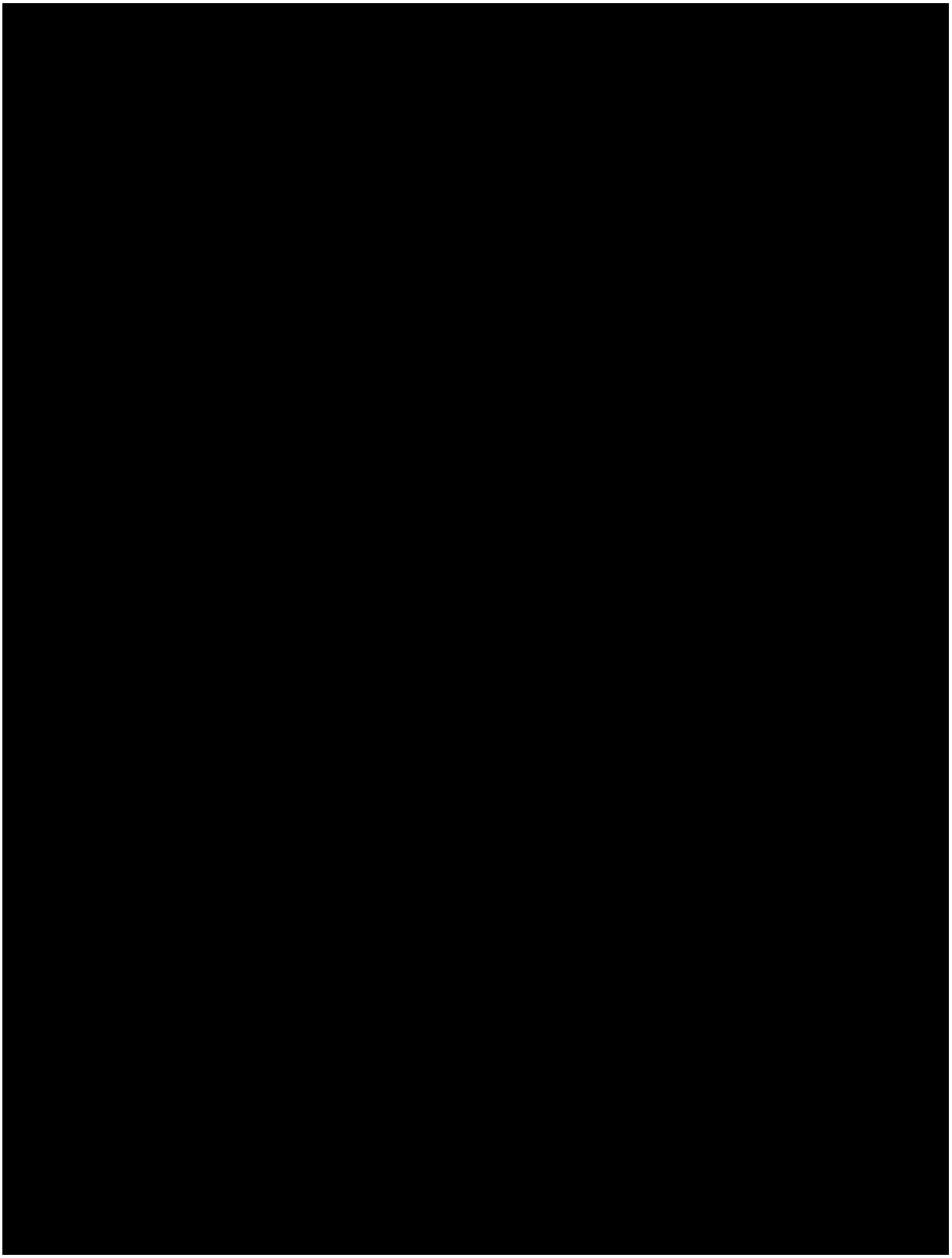

Figure 6. ERG base case extrapolations of OS, MFS and ToT for the a) darolutamide plus ADT and b) ADT arms

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

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

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

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by the end of **5 June 2020** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Inaccuracies

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr><td>Brand name of darolutamide spelled incorrectly.</td><td>Please amend the brand name to NUBEQA® throughout the report.</td><td>Incorrectly spelled brand name.</td><td>Brand name of darolutamide has been checked and amended.</td></tr>
<tr><td>In the ERG report Section 1.5, Table 3, for the scenario (based on the ERG preferred base case) assuming an average of Nov 2019 generalised gamma and Weibull distributions for darolutamide OS (using switch in cell H22 on the “ERG” sheet), the reported results do not align with those of the model</td><td>
<table>
<tr><td rowspan="2">Description</td><td colspan="3">Darolutamide + ADT</td><td colspan="4">ADT alone</td></tr>
<tr><td>Costs</td><td>QALY</td><td>LYG</td><td>Costs</td><td>QALY</td><td>LYG</td><td>ICER vs ADT</td></tr>
<tr><td>Average of Nov 2019 generalised gamma and Weibull for darolutamide OS</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£8,529</td></tr>
</table>
</td><td>This error needs correction to accurately illustrate the effect of choosing the model averaging approach suggested by the ERG on the new ERG preferred base case ICER.</td><td>The analysis is as the ERG intended. It takes the average of the generalised gamma and Weibull for extrapolation of OS in the darolutamide arm, instead of applying an equalised mortality assumption from a fixed future time point. The equalisation of mortality switch must be turned off for this analysis, and the ICER matches.

We have added clarification in the table.</td></tr>
</table>

In Section 5.1, Table 24 of the ERG report, the percentage changes to the ICER comparing the original company base case versus the revised company base case are not accurately reported.	Scenario	ICER (£/QALY): darolutamide +ADT versus ADT	Percentage change to ICER	This error needs correction to accurately illustrate the percentage change to the ICER.	The correction is accepted. The error followed from a typo in the ERG table, stating an original base case ICER of 11,455 rather than 11,445.
	Submitted company model base case	£11,455			
	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%***		

	viii. Amendments for costing ongoing background use of ADT	£11,835	***3.41%***		
	Revised company base case incorporating all changes	£4,919	***-57.02%***		

Issue 2 Clarifications

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Claims around the OS benefit of darolutamide *1.* In the ERG report, page xv of the executive summary, one of the main issues raised around the clinical effectiveness is that '*The ERG is questioning whether there is a benefit on OS from darolutamide. 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.* *2.* This is continued with *'The ERG is also of the opinion that the benefit shown in the ARAMIS trial is being*	The company kindly requests clarification on 1. whether the ERG is questioning the OS benefit of darolutamide or whether it is the generalisability of the OS benefit observed in ARAMIS that is being questioned; 2. why the ERG suggests the benefit shown in ARAMIS is being driven by the proportions of participants who received a subsequent treatment; 3. how the ERG suggests dealing with the implied confounding effect on the OS benefit stemming from the difference between the subsequent treatment distributions observed in ARAMIS and the ones expected in UK practice. The company also asks for the rewording of the relevant paragraphs accordingly in line with the above clarifications and that any unsubstantiated claims to be	1. The company believes that questioning the significance of darolutamide's OS benefit is unwarranted and not aligned with the available evidence. It has been clearly demonstrated in a high-quality international double-blind placebo-controlled trial, ARAMIS, that darolutamide + ADT offers a statistically significant OS benefit (i.e. 31% risk reduction, HR=0.69) compared to ADT alone in patients with nmCRPC. While it is true that the median has not been reached at the final data-cut in either arm (the control arm being closer to the median) and many patients are still contributing a censored survival time, this is something to be expected given the early stage of the disease and the reduced mortality risk of darolutamide. 2. The company does not share ERG's opinion that *'the benefit shown in ARAMIS is being driven by the proportions of participants who received a subsequent treatment'*. The proportions of patients receiving subsequent treatment in ARAMIS was fairly balanced between the arms: most common subsequent treatments being docetaxel 62% vs 53%, enzalutamide 25% vs 28%, and abiraterone 26% vs 31% in the	The text in the report has been revised to make the ERG's points clearer. The view of the ERG is that the OS benefit shown in the ARAMIS may not be generalisable to UK clinical practice. The reasons for this are the differences in use of subsequent treatments for participants who progress and also the relatively low proportion of progressing participants who do receive a subsequent treatment. The ERG note that the company have presented the results from using rank preserving structural failure time model and iterative parameter estimation to adjust for crossover between placebo and darolutamide. The company could potentially make use of these methods, or the two-stage accelerated failure time model or inverse probability of censoring weights, to adjust out the effects of all subsequent treatments received. They could

driven by the proportion of participants who received a subsequent treatment.' *3.* The ERG is also stating '*Moreover, the proportions of patients who received subsequent treatments are not entirely in line with those observed in the UK clinical practice.*' Also, on page 23 in section 3.2.2, the report states *'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*	removed.	intervention and control arms respectively. Moreover, most patients would have received their subsequent treatment in the double-blind phase of the trial i.e. resulting in a randomised and blinded subsequent treatment allocation. Therefore, the subsequent therapy received is not a confounding factor of the OS benefit observed in ARAMIS. In fact, patients in the control arm received a relatively higher proportion of enzalutamide and abiraterone and were also allowed to switch over to the darolutamide arm following unblinding (a total of [redacted] patients); in this respect, the OS benefit observed is probably conservative. 3. The company understands ERG's concerns around the differences in subsequent treatments used in ARAMIS and what would be expected in UK clinical practice once patients progress to metastatic disease which it is argued limit the generalisability of the OS benefit observed (i.e. higher use of enzalutamide/abiraterone and lower use of docetaxel following ADT, and potentially no use of enzalutamide/abiraterone and higher use of docetaxel following darolutamide). However, the company kindly asks the ERG to consider the following issues when acknowledging this limitation: a. In international RCTs it is unlikely for subsequent treatments to	then simulate the efficacy of the proposed subsequent treatment pathways in the context of an economic Markov model that separates out post-progression survival and allows it to be influenced by the subsequent treatments modelled (see below). Please note that we are not suggesting that no OS benefit would be seen in the NHS pathway, but we wish to highlight the uncertainty related to OS and question the magnitude of it. Our point is that more patients would move quickly upon progression in the ADT arm to enzalutamide or abiraterone, whilst those progressing on darolutamide would only be able to have docetaxel, cabazitaxel or radium-223. <u>On the ERGs economic modelling of OS.</u> Given the greater number of more efficacious subsequent treatments available on the NHS to patients who progress on ADT alone, it is the ERGs opinion, in line with previous nice appraisals (TA580, TA377 and TA387), that post-

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.		accurately reflect that of a given country, yet it is acknowledged that the most used subsequent treatments in ARAMIS are also the ones most commonly used in UK clinical practice, but their distributions are likely to differ. However, the fact that the UK positioning of darolutamide is likely to shift the use of the androgen receptor inhibitors (ARIs) drug class earlier in the treatment pathway (i.e. from first line in mCRPC to nmCRPC patients before progressing) makes such imbalances observed between the subsequent treatment distributions in ARAMIS and UK practice unavoidable in the context of a randomised controlled trial. b. Radium-223 is another efficacious treatment commonly used in UK practice but which has not been included as a subsequent treatment in ARAMIS. A large sample of clinical experts (10 oncologists and 1 urologist) that participated in the clinical validation advisory board organised by Bayer in February 2020 suggested a higher subsequent radium-223 use in the darolutamide arm for	progression survival would be expected to be somewhat higher in the ADT arm compared to the darolutamide arm; i.e. for the estimated proportion progressing to the mCRPC state, remaining life expectancy should be higher in the ADT arm from the point of progression. We were guided by this when selecting a base case extrapolation for OS. With the ERG preferred extrapolation of MFS (chosen to address inconsistency between data cuts for MFS and TTD) and the diverging Weibull OS curves, we found that mortality in the darolutamide arm had to be equalised to the ADT arm prior to 7 years to satisfy this assumption. Otherwise, the model would infer that post-progression survival is higher in the darolutamide arm. To illustrate: With the ERG curve selections, undiscounted mCRPC life years, divided by the estimated proportion making the transition to mCRPC, is higher in the darolutamide arm when mortality is equalised from 7 years. When mortality is equalised from 5 years, approximated post-progression

		eligible patients. Thus, the potential benefit of radium-223 on the OS in the darolutamide arm is not captured in the ARAMIS data, potentially underestimating the true OS expected in UK practice, which is similar with ERG's concern around the low use of enzalutamide/abiraterone in the ADT arm. c. The company has already presented some evidence from further analyses that split the OS data by subsequent treatment line (see response to clarification question B7); these showed inconclusive results regarding the OS impact of the subsequent treatments received, with the overlapping confidence intervals suggesting there is no significant difference. In light of the above issues, the company considers the ERG's approach of dealing with the outstanding uncertainty in the OS benefit (i.e. by applying a 5 year cut-off to the benefit) to be unrealistic and overly conservative and disproportionately impacting darolutamide. A large sample of clinical experts (10 oncologists and 1 urologist) that participated in the clinical validation advisory	survival is slightly higher in the ADT arm, satisfying the assumption outlined above. Therefore, the ERG does not believe their base case OS assumptions are implausible – unless there is justification/evidence to suggest that darolutamide will lead to a long-lasting relative OS benefit that is maintained to some extent through the mCRPC health state, despite the fewer subsequent treatment options available. The company have not demonstrated this. The ERG acknowledges the uncertainty, and have offered two alternative OS extrapolation options that are more conservative than the company's base, but more favourable to darolutamide than the ERG base case. The ERG also agrees with the company that more explicit adjustment of OS for expected subsequent treatments would be a preferable way to address the uncertainty. Upon reflection, it is the ERGs opinion that these complexities may be better addressed using a state

			board organised by Bayer unanimously agreed that a 5-year cut-off is too conservative. In the previous appraisal of enzalutamide in nmCRPC (TA580) a cut-off of 8.7 years was applied by the ERG in the context of PROSPER data not showing a statistically significant difference at that time. The company is willing to explore additional valid ways of formally adjusting the OS data that the ERG may wish to suggest. The cost-effectiveness model submitted by the company uses the best available evidence in line with NICE methods and has been extensively validated by clinical experts. The company considers the theory of darolutamide not resulting in an OS benefit when used earlier in nmCRPC in UK practice is not supported by the available evidence. Ultimately, ARAMIS, PROSPER and SPARTAN are the only evidence sources for OS following ARI treatment in the nmCRPC setting and they all now conclude statistical significance in OS; each trial has a different set of subsequent treatments and all show that this shift in treatment paradigm	transition model that accounts for the relationship between progression and mortality, and the efficacy of the subsequent treatments available to patients. A sentence has been added to section 1.3, first bullet 1, to reflect this. In a further point relating to the model structure and assumptions, the ERG believes the company's current approach could potentially underestimate the proportion expected to transition to the mCRPC state, and the application of medians to model expected subsequent treatment durations could underestimate subsequent treatment costs in PD1 but overestimate progression through to subsequent lines of therapy. A Markov state transition model would be better placed to address such issues.

		increases survival.	
In the ERG report Section 3.2 page 23, it was stated that "*The ERG's clinical expert opinion is that darolutamide, which is a similar class of drug to enzalutamide, would not be expected to provide a significant OS benefit in clinical practice".*	The company requests clarification concerning the clinical expert's statement on the significant OS benefit. Specifically, whether the recent data showing significant improvement in OS is considered in this opinion.	In addition to presenting significant OS benefit results from ARAMIS in the company submission (see Appendix N), results from Phase III PROSPER trial have shown statistically significant improvement in OS in patients with nmCRPC that were treated with enzalutamide compared with patients on the ADT arm.[1]	We have slightly revised our statement as follows: *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 treatment pathway used in the NHS.* As explained earlier, it is the generalisability of the OS benefit and its magnitude that is in question.
In the ERG report Section 3.6 page 35, it was stated that the "*The ERG agrees with this approach to use proportions suggested by the company's Advisory Board, which are more reflective of UK clinical practice and also to consider fitting parametric survival curves separately."* This statement is unclear regarding what separate parametric survival curves should be considered to be fitted.	The company would like to ask for clarification on the recommendation to consider fitting parametric survival curves separately, so that this uncertainty can be best addressed by the company.	Clarification	Please note that this was not written as a criticism. We agree with the company's decision to use proportions suggested by the Advisory Board. We are also in agreement with the approach of fitting parametric curves for the control and intervention arms separately. The text in the report has been revised to make this clear.

Issue 3 Typographical/grammatical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Typographical error in Section 1.5 title in Table 3.	"***Scenario*** *analyses undertaken on the ERG base case*"	Resolving a typographical error	The typographical error has been corrected.
Grammatical error in Section 2.2 page 1.	"*Stages of prostate cancer are classified based* ***on*** *responsiveness to hormonal therapy*"	Resolving a grammatical error	The grammatical error has been corrected.
A broken cross reference referring to a table in Section 3.2 page 13 .	"*The proportion of study participants receiving anticancer therapy for metastatic CRPC after discontinuing study treatment is summarised in* ***Table 8*** *below*."	Resolving a cross referencing error	The cross referencing error has been corrected.
Typographical error in Section 4.2 page 38.	Delete ***32***	Resolving a typographical error	We could not find this typo on page 38.
Typographical error in Section 6.1 Table 27 scenario 8.	*"Equalise mortality risk in the ADT arm to the mortality risk in* ***the darolutamide*** *arm from 5 years"*	Resolving a typographical error	The typographical error has been corrected.
Typographical error in Section 6.1 Table 27 scenario 13.	*"Alternative monitoring costs (****TA580****) with revised unit costs for consultant oncology visits and ADT administration"*	Resolving a typographical error	The typographical error has been corrected.

References:

1. Pfizer. XTANDI® (ENZALUTAMIDE) DEMONSTRATES SIGNIFICANT IMPROVEMENT IN OVERALL SURVIVAL IN PHASE 3 PROSPER TRIAL OF PATIENTS WITH NMCRPC. 2020. Available at: https://investors.pfizer.com/investor-news/press-release-details/2020/XTANDI-enzalutamide-Demonstrates-Significant-Improvement-in-Overall-Survival-in-Phase-3-PROSPER-Trial-of-Patients-with-nmCRPC/default.aspx. Accessed: 03 06 2020.

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Technical engagement response form

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

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **6 August 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Bayer plc**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Questions for engagement

Issue 1: **Treatment pathway**	
Is the company's assessment of the current treatment pathway and likely treatment pathway if darolutamide is available reasonable? (see table p11 technical report) In particular, after having darolutamide for non-metastatic disease is it likely that: • no one is offered enzalutamide for metastatic disease • fewer people than currently are offered abiraterone for metastatic disease • more people than currently are offered docetaxel for metastatic disease?	The treatment pathways proposed have been derived through the consensus of a large panel of clinical experts from across the UK (comprising of nine oncologists and one urologist) that participated in the clinical validation advisory board organised by Bayer in February 2020[1]. The pathways proposed accurately reflect current UK prescribing patterns once patients progress to mCRPC as well as how these patterns would change following the introduction of darolutamide for the treatment of nmCRPC. The proposed treatment pathways were again discussed in a separate advisory board organised by Bayer in July 2020 with 8 UK clinical experts[2]. All experts supported the treatment pathways derived in February 2020, with the comment that radium-223 may have an increased use in earlier lines in mCRPC, in the short-term at least, due to its temporary inclusion on the CDF COVID-19 medicines list for use before docetaxel.
Why would enzalutamide and abiraterone not be used after darolutamide?	While darolutamide has a distinct molecular structure compared to enzalutamide, the mode of action is similar and the clinical opinion is that the sequential use of these agents is prone to cross-resistance and may not offer added clinical benefit[1,2]. Evidence on the sequential use of darolutamide and enzalutamide is lacking, but evidence on the sequential use of enzalutamide and abiraterone is not promising and shows very low response rates[3-6]. Despite both agents having different mechanisms of action, the clinical data suggests significant cross resistance and clinical opinion is that similar cross resistance would be found in the newly mCRPC setting for patients who have progressed form the nmCRPC setting on similar/identical agents (i.e. Darolutamide/Apalutamide/Enzalutamide)[2]. Clinical opinion is therefore that other treatments (such as docetaxel) are more likely to be effective following progression on darolutamide, and would be used in preference to enzalutamide/abiraterone[2]. Additionally, clinical opinion suggests that while many patients do respond to newer anti-androgen therapies, a subset of patients

	progress within a year or less, representing a more aggressive disease phenotype that may benefit from chemotherapy rather than another anti-androgen[2]. Moreover, NHS England commissioning policy suggests that either enzalutamide or abiraterone should be used only once in the treatment pathway; the proposed treatment pathways are also broadly aligned with previous appraisals[7].
Issue 2: Generalisability of ARAMIS to UK practice	
The table on p12 of the technical report shows the subsequent treatments in ARAMIS and those modelled by the company, which the company suggests reflects likely NHS practice. • Are abiraterone or enzalutamide taken after darolutamide expected to be effective compared with docetaxel or with best supportive care? Would these treatments be offered after darolutamide in NHS clinical practice? • Are overall survival estimates from ARAMIS likely to underestimate survival for ADT alone because fewer people had abiraterone or enzalutamide after ADT alone than is seen in NHS clinical practice?	There is currently limited evidence on whether the use of abiraterone or enzalutamide after darolutamide or ADT would provide a distinct survival benefit compared to docetaxel, but the anecdotal evidence available and clinical expert opinion suggests there is unlikely to be an important difference between these agents following ADT and response rates are expected to be worse with enzalutamide and abiraterone compared to docetaxel following darolutamide due to cross-resistance. In an advisory board held on 16 July 2020,[2] the clinical experts stated that docetaxel, abiraterone and enzalutamide have a comparable survival benefit versus BSC in the metastatic setting; the experts noted the fairly similar hazard ratios in the respective trials for docetaxel (0.76 [95% CI 0.62-0.94]),[8] abiraterone (0.81 [95% CI 0.70-0.93])[9] and enzalutamide (0.71 [95% CI 0.60-0.84])[10]; differences in median survival were attributed to the differences in the trial settings as they were conducted a number of years apart. This is also supported by the exploratory analyses of ARAMIS overall survival data split by the subsequent therapies abiraterone, enzalutamide and docetaxel for both the darolutamide and ADT arms, presented in response to question B7 of the ERG clarification questions. While acknowledging that the ARAMIS trial was not powered to detect the differences in any subsequent treatment effects, the analyses demonstrated that survival on these subsequent therapies did not significantly differ, with KM curves and their confidence intervals overlapping throughout. In the advisory board held on 4 February 2020,[1] the nine practicing UK clinicians agreed that enzalutamide would not be given at any line of therapy following progression on the darolutamide + ADT arm and abiraterone would only be given to a very small number of patients. In the advisory board held on 16 July 2020, clinicians also expressed their concerns regarding the effectiveness of enzalutamide/abiraterone if taken after darolutamide.[2] Additional expert input (reflected in Appendix 3 of the July 2020 advisory board minutes) suggested in fact that

	response rates are expected to be better for docetaxel or alternative agents like radium-223 compared to enzalutamide/abiraterone if taken after progression on darolutamide, particularly in patients with aggressive phenotype disease that are expected to progress early[2]. Therefore, we believe that enzalutamide would not be offered, and abiraterone would rarely be offered to patients in the metastatic setting in the NHS clinical practice. As ARAMIS was an international double-blind randomised controlled trial, physicians were permitted to treat patients with all active therapies approved in the metastatic setting, being indeed blinded to the initial treatment allocation when the subsequent treatment decision was being made. As a result, a proportion of patients in the darolutamide arm received subsequent treatments that are not commonly prescribed in the NHS clinical practice. The cross-over also explains the low use of abiraterone/enzalutamide in the ADT arm at the final data-cut of ARAMIS, as the remaining progression-free patients on ADT would have received darolutamide during the open-label phase of the trial, prompting a relatively higher subsequent use of docetaxel following progression. Unfortunately, there are no long-term survival data for nmCRPC patients and no survival data reflecting the subsequent treatments received in UK clinical practice. However, compared to other recently published anti-androgen therapy trials in nmCRPC with a longer follow-up, the estimated median OS for darolutamide and ADT arms from the cost-effectiveness model (using the company's base case) of 71.75 and 59.79 months, respectively, are largely aligned with the median OSs for patients in the SPARTAN trial[11] of 73.9 vs. 52.8 months and PROSPER trial[12] with a reported median OS of 67 vs. 56.3 months for apalutamide vs. ADT and enzalutamide vs ADT, respectively. In summary, the cost-effectiveness model results based on ARAMIS demonstrated that overall survival in men with non-metastatic castration resistant prostate cancer is significantly improved in the darolutamide arm with a favourable safety profile despite the significant crossover (170 patients) to the darolutamide arm. Although patients in the darolutamide arm in ARAMIS received subsequent treatments not reflective of UK clinical practice, this is not thought to over-estimate their overall survival. On the contrary, clinical expert opinion suggests that based on the anecdotal evidence on the sequential use of androgen receptor targeted agents (i.e. abiraterone/darolutamide/enzalutamide/apalutamide), response rates to chemotherapy or alternative agents such as radium-223 are expected to be better than to enzalutamide/abiraterone for patients progressing on darolutamide[2]. Radium-223, which has been demonstrated to be a life-extending therapy in mCRPC, would indeed be prescribed in UK

	practice (relatively more following progression on darolutamide), but it was not among the subsequent therapies used in ARAMIS, while the use of chemotherapy following darolutamide in ARAMIS was lower than what would be expected in UK clinical practice. Therefore, the overall clinical experts' opinion suggests the OS for the darolutamide arm in ARAMIS is likely to underestimate the expected survival in the UK as relatively more patients were treated with abi/enza instead of docetaxel following progression on darolutamide; these agents are likely to be less effective and this would provide an opportunity for the cancer to progress on treatment and patients to subsequently become ineligible for chemotherapy or radium-223 due to a drop in performance status[2]. It is currently unclear whether the change in subsequent therapy use to reflect UK clinical practice for the ADT arm would drastically impact overall survival estimates, but given that docetaxel/enzalutamide/abiraterone all demonstrated similar improvements in OS in the mCRPC setting and that clinical opinion suggests they are equally effective in practice[2], the relatively lower use of enzalutamide/abiraterone compared to docetaxel after ADT in ARAMIS is unlikely to underestimate the OS expected in clinical practice. Further clinical opinion suggests that in practice clinicians tend to use abiraterone/enzalutamide first due to the lower toxicity levels and the impact on quality of life compared to chemotherapy, but these agents are expected to be equally effective as chemotherapy when it comes to OS[2]. Overall, clinical experts suggest that patients would still have access to a range of effective treatment options after progression to darolutamide including docetaxel, cabazitaxel, radium-223, potential re-challenge with docetaxel, or other developing agents, hence survival with metastases is not expected to be impacted much if at all in practice. Moreover, clinical experts suggest that the 170 patients that crossed-over to the life-extending darolutamide during the open-label phase of the study would have likely overestimated the OS of the ADT arm in ARAMIS compared to the current clinical practice[2]. Based on the arguments above, the company believes the relative OS benefit observed in ARAMIS and modelled in the cost-effectiveness analysis is likely to be conservative, underestimating the expected benefit in UK clinical practice due to 1) the use of cross-resistant agents following progression to darolutamide and 2) the cross-over of patients from the ADT arm to the darolutamide arm in ARAMIS. Additionally, clinical experts stated that the survival with metastatic disease is unlikely to be impacted much, if at all, in clinical practice as a result of shifting the use of androgen receptor targeted agents earlier in the treatment pathway as this has been demonstrated to increase overall survival and would potentially allow more patients to

	benefit from other effective treatment options as early as metastases develop and before their performance status deteriorates[2].
Issue 3: Maturity of overall survival data	
Are there any long-term data for survival in people who had darolutamide + ADT or ADT alone for non-metastatic hormone-relapsed prostate cancer?	The November 2019 data-cut was the final planned analysis for the overall survival of patients in ARAMIS. Unfortunately no studies were identified in the systematic literature review where the long-term overall survival for patients diagnosed with non-metastatic castrate resistant prostate cancer was reported. However, as discussed in the response to issue 2, the estimated median OS for the darolutamide and ADT arm from the cost-effectiveness model using the company's base case of 71.75 and 59.79 months, respectively are comparable to the recently published median OS for patients in the SPARTAN trial[11] of 73.9 vs. 52.8 months and PROSPER trial[12] with a reported median OS of 67 vs. 56.3 months for apalutamide vs. ADT and enzalutamide vs ADT, respectively, where all three trials have comparable trial design and patients populations. Therefore, the longer follow-up in SPARTAN and PROSPER which both had mature data demonstrates the validity of the modelled OS based on ARAMIS.
Issue 4: Clinical trial data used in the model	
Would most people continue darolutamide until their cancer metastasised?	In the ARAMIS trial, patients discontinued due to metastasis, adverse events, judgement of investigator, personal choice, or protocol deviation. As reported in section B.2.10 of the company submission, 8.9% of darolutamide+ADT patients discontinued study treatment due to AEs in the darolutamide + ADT group (compared to 8.7% of patients in the placebo group), suggesting that not all patients continue treatment until metastasis. Patient choice is also a factor in the decision to continue treatment until metastasis in the real world setting and may play a role in stopping treatment prior to this, particularly in the context of long-term treatment. In ARAMIS, discontinuation due to personal choice and judgement of investigator often related to safety concerns or suspected metastases but due to the nature of the data collection (i.e. free-text, not discrete) and the definition of MFS and safety endpoints, a formal analysis was not pre-planned or performed. These reasons would constitute valid reasons for discontinuing treatment in clinical practice.

In absence of metastasis-free survival data from the November 2019 data cut, is the ERG approach of using a Gompertz curve to align metastasis-free survival with time on darolutamide treatment appropriate?	No further MFS analyses were pre-planned past the October 2018 primary analysis data-cut as per the Statistical Analysis Plan of ARAMIS. The company believes that the September 2018 data are still the best for MFS extrapolation and should not be altered due to changes in other outcomes: the Gompertz extrapolation lacks clinical validity and showed a poor statistical fit; also, further analysis of time to subsequent antineoplastic therapy, which is expected to be highly correlated with MFS, showed no difference in risk between the data cuts. In the absence of updated independent metastasis assessments, we have compared the time to initiation of subsequent antineoplastic therapy between data cuts, as this was suggested by all clinical experts to be the most appropriate proxy measure (of those available from the November 2019 ARAMIS data cut) to reflect metastatic progression.[2] As shown in Figure 1 and Figure 2, although there is an increase in risk of treatment discontinuation for patients on the darolutamide arm in the November 2019 data cut, there is little difference across the data cuts (apart from longer follow up) of risk of subsequent antineoplastic therapy in either treatment arms. **Figure 1: Time on treatment compared at 03SEPT2018 and 15NOV2019 - Kaplan-Meier** 

[redacted]

Figure 2: Initiation of subsequent antineoplastic therapy compared at 03SEPT2018 and 15NOV2019 - Kaplan-Meier

In summary, when considering time to initiation of subsequent antineoplastic therapy as a proxy measure for disease progression, the KM curves show that there is not enough evidence to conclude that there is a shift in the shape of the curves. Moreover, in the advisory board held on 4 February 2020,[1] the nine practicing UK clinicians stated that the extrapolation of the September 2018 MFS data using the Weibull curve is the most plausible and a conservative distribution for both arms, and is in line with what is currently observed in clinical practice. Furthermore, the clinicians considered that the Gompertz curve lacks clinical face validity projecting that 0% of patients will be in the metastatic free state at 5 years.[1]

	Based on the summarized evidence above, the company considers the Weibull curve to be the most appropriate curve to model MFS for both treatment arms as validated by clinical experts in the validation meeting.[1]
Company please provide metastasis free survival from the November 2019 data cut if available.	No additional independent measures of metastatic progression were conducted after the September 2018 data cut; therefore, no further MFS analyses were planned and conducted as part of the November 2019 data-cut. This reflects the Statistical Analysis Plan of ARAMIS.
Issue 5: Approach to modelling time on subsequent treatments after disease metastasis	
Company please provide a scenario in which consistent durations on 1st, 2nd and 3rd treatments for metastatic prostate cancer are used when applying weighted costs and utility values in the model	In order to align cost-effectiveness model inputs for time in subsequent metastatic health states (which inform both treatment costs and QALYs/utilities), we have explored additional scenarios, where the same inputs are used to inform both cost and utility calculations for the mCRPC state. The amendments for this scenario have been made in sheets "Subseq_Trt" row 28 and columns C90-M98 in the cost-effectiveness model (version 3.0) and the switch has been added to cell I116 of the "Control" sheet. The three scenarios that have been added to the model, and user inputs are as follows: • Alternative scenario 1: the time of progression to subsequent lines of therapy used to calculate the weighted subsequent treatment costs was based on estimated LYs from TA377 (also used to calculate weighted utility values), rather than weighted median time on treatment data. • Alternative scenario 2: the difference in average time of progression using reported median MFS from appropriate literatures[13-17] (added in "Subseq_Trt" sheets in cells F91-F98) for each subsequent therapy were weighted and used to estimate the LYs spent within each subsequent state (and the proportion of patients reaching subsequent mCRPC states) and the weighted utility in each arm based on the published utilities in SMC No. (1066/15)[18] • Alternative scenario 3: the difference in average time of progression using mean MFS (rather than median MFS) is used to estimate the LYs spent within each subsequent state and the weighted utility in each arm. In this approach, the mean MFS (displayed in

"Subseq_Trt" sheets in cells G91-G98, respectively) were estimated using reported median MFS while assuming an exponential distribution.

Given that durations and costs of treatment are typically positively skewed due to some patients incurring higher duration and costs as a result of various medical factors, in addition to aligning inputs to use mean/median mCRPC LYs, we have explored the option of using the estimated mean ToT to inform weighted subsequent treatment costs, rather than median ToT, which is likely to underestimate the true costs of subsequent treatments. The amendment has been made in Sheets "Subseq_Trt" columns E90-E98 and "Parameters" columns D43- D50. The switch for this scenario has been added to cell I118 of the "Control" sheet. In this approach, as suggested by the ERG during the technical engagement call, the mean ToT was estimated using reported median ToT while assuming an exponential distribution.

All scenarios were run using the company base case submitted in response to the ERG clarifications while adopting alternative scenario 3 to estimate the time to next subsequent therapy and mean ToT to estimate subsequent treatments costs as the new base case. The company considers that using mean MFS/ToT to estimate the time to next subsequent treatment and costs are more accurate given that the median underestimates the true duration and costs given their positive skewness. As detailed in Table 2, the adjustments resulted in a small increase when applying consistent assumptions for the weighted utility and cost calculations. However, when using the mean ToT to estimate time to next subsequent treatment in the updated company base case, this resulted in a moderate increase in the ICER. When the mean ToT was used to estimate the average one-off drug costs, the ICER moved to the south east quadrant where darolutamide is dominant, due to the increased subsequent therapy costs.

Table 1: Results of time to next subsequent treatment methods scenario analysis

Time to next subsequent treatment approach (utility and cost)	Assumption for subsequent treatment durations (cost)	ICER (£/QALY): darolutamide+ADT versus ADT
Company model base case (as per response to ERG clarification questions)		**£4,919**

Company alternative scenario 1	Median TOT	£5,194
Company alternative scenario 2	Median TOT	£5,226
Company alternative scenario 3	Median TOT	£6,542
Company alternative scenario 1	Mean TOT	Darolutamide dominant
Company alternative scenario 2	Mean TOT	Darolutamide dominant
Company alternative scenario 3 (updated company base case)	**Mean TOT (updated company base case)**	**Darolutamide dominant**
Key: ICER, incremental cost-effectiveness ratio; ToT, time on treatment; ADT, androgen deprivation therapy.		

Additionally, in response to the ERG's comment in the technical engagement call, we have considered a different approach to estimate the time on treatment for ADT in the mCRPC state whereby we have sourced the median time on treatment of the ADT arm in the PREVAIL study for patients in the mCRPC state.[19] The amendment has been made in Sheets "Subseq_Trt" cells D92 and F92. The switch for this scenario has been added to cell I120 of the "Control" sheet. As shown in Table 3, this scenario resulted in a slight increase in the ICER.

Table 2: Results of time on treatment for ADT scenario analysis

Time to next subsequent treatment approach (utility and cost)	**Assumption for ADT treatment duration (cost)**	**ICER (£/QALY): darolutamide+ADT versus ADT**
Updated company model base case		**Darolutamide dominant**
Updated company model base case	External data	Darolutamide dominant

	Company model base case (as per response to ERG clarification questions)		**£4,919**
	Company model base case (as per response to ERG clarification questions)	External data	£4,989
	Key: ICER, incremental cost-effectiveness ratio; ADT, androgen deprivation therapy; ERG, evidence review group.		

Issue 6: Monitoring costs	
Which monitoring assumptions better reflect NHS clinical practice, the company's or the ERG's? (see table p13 technical report)	In the NICE technical report, it is stated that 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. Thus, the ERG prefers resource use frequencies based on TA580, which are based on the ERG report of the NICE appraisal TA377[14] of enzalutamide in pre-chemo mHRPC. This assumes equal resource use across nmCRPC and mCRPC health states. However, as discussed in the company's submission document Section B.3.5, no healthcare resource use frequencies for patients in the nmCRPC states were identified in the UK clinical settings in the healthcare resource use systematic literature review. As such a study, funded by Bayer and led by IQVIA, was conducted to understand healthcare resource use and costs of nmCRPC patients prior to and following occurrence of metastasis.[20] The company considers these frequencies to be more reflective of the healthcare resources use frequencies of patients in the nmCRPC state in the UK clinical practice, being derived in an actual healthcare resource utilisation study. This was further validated in the clinical ad-board held on 16 July 2020[2]: when looking at the multidisciplinary team as a whole, the advisors explained that patients with mCRPC will likely have more appointments than patients with nmCRPC, as patients with mCRPC have greater symptoms, worse quality of life and are more likely to experience complications and primary care interventions than those with non-metastatic disease. Additionally, it was stated that patients are

	scanned much less frequently than every 12 weeks in the nmCRPC setting in current practice, and that patients in the metastatic setting would be scanned much more frequently than those in the nmCRPC setting.
What is the cost of a consultant-led outpatient appointment: £194 (ERG estimate) or £109 (company estimate)?	As detailed in the company's submission Section B.3.5, the outpatient consultant appointment was sourced from the latest PSSRU 2019.[22] This is line with the accepted approach in TA580[7] and TA377[14] where the PSSRU costs were also used to source the outpatient consultant appointment cost. As such, in line with the accepted costing approaches in TA377[14] and TA580[7], the company considers the consultant-led outpatient sourced from the PSSRU to be appropriate.
Issue 7: Plausibility of company modelled outcomes: extrapolation of overall survival estimates from trial data	
Are there any data to validate the company's long-term overall survival extrapolations?	Please refer to the company responses to issues 2 and 3. In summary, the estimated median OS for the darolutamide and ADT arm from the cost-effectiveness model using the company's base case of 71.75 and 59.79 months, respectively are comparable to the recently published median OS for patients in the SPARTAN trial[11] of 73.9 vs. 52.8 months and PROSPER trial [12] with a reported median OS of 67 vs. 56.3 months for apalutamide vs. ADT and enzalutamide vs ADT, respectively where all three trials have comparable trial design and patients population.
Would you expect any people to be alive?	In the advisory board held on 16 July 2020,[2] the practicing UK clinicians considered it possible that a small proportion of patients treated with darolutamide would survive ~20 years in clinical practice. This is reflected in the company's base case assumptions, with 2.35% and 0.02% of patients surviving to 20 years on the darolutamide+ADT and ADT arms, respectively.
Issue 8: Plausibility of company modelled outcomes: time in metastatic health state	
Is it plausible that the survival benefit in the metastatic health state would be longer after darolutamide + ADT than ADT alone? Is there a treatment benefit after stopping darolutamide?	In the advisory board held on 16 July 2020[2], clinicians stated that the focus of treatment efficacy should be on how long patients are asymptomatic as early efficacious treatments can affect the subsequent aggressiveness and progression of the metastatic disease and therefore post-progression survival. As such, clinicians suggested that (conditional) survival from the point of metastatic progression is an artificial point with no relevance in clinical practice.[2]
Given that there may be more treatment options available after ADT alone, would it be expected that	

survival with metastatic prostate cancer is longer after ADT alone after than after darolutamide + ADT?	As stated above, clinicians at the 16 July advisory[2] board stated that effective treatments in early disease, such as darolutamide, are expected to affect the progression within the metastatic disease. However, the difference between the post-metastatic survival of patients starting on darolutamide+ADT and ADT alone is unclear. As illustrated in Figure 3, we do not observe a significant difference in the post-progression survival in the ARAMIS trial between arms, acknowledging that this analysis is associated with a high level of uncertainty and that the post-metastatic survival in the ADT arm is likely confounded by the 170 patients crossing over and receiving darolutamide before progression. **Figure 3: Post-metastatic survival for the darolutamide + ADT and ADT arms, September 2018 data-cut where patients with metastasis at baseline were censored**  To realise this potential change in treatment effect over time in the model, a treatment effect cut off is added as an option. In the advisory board held on 4 February 2020, the nine practicing UK clinicians[1] stated that it would be overly conservative to assume an equal mortality risk for both arms after trial follow-up in the model base case, and that a survival benefit for darolutamide
Are the ERG's scenarios appropriate for addressing uncertainty? Would there be no relative survival benefit with darolutamide + ADT over ADT alone after 5 years?	

could be observed over a number of years as early efficacious treatment can also affect the subsequent progression of the metastatic disease.

Moreover, in the advisory board held on 16 July 2020,[2] the practicing UK clinicians indicated that if survival of patients with metastatic disease following progression on darolutamide + ADT were indeed be conservatively assumed to be impacted negatively, it would not be expected to be impacted any worse than 3-4 months less than those on progressing on ADT alone. An impact higher than that lacks face validity as neither enzalutamide or abiraterone demonstrated an impact on OS in mCRPC higher than that based on their respective clinical trials.[9, 10]

Table 4 below illustrates the difference in patients' survival following metastatic progression between the ADT and darolutamide + ADT arms using different survival benefit assumptions. The results below are run using both the company's updated base case (Weibull curve for MFS extrapolation of both treatment arms and updates as described above in issue 5) and the ERG preferred assumptions (Gompertz curve for MFS extrapolation of both treatment arms) whilst using the ERG's suggested approach when applying treatment waning (adjusting the darolutamide + ADT arm using the ADT arm).

Table 3: Results of survival benefit cut-off scenario analyses

Survival benefit cut-off	**Assumption for MFS extrapolation**	**PPS survival difference (months): darolutamide+ADT vs ADT**
Updated company model base case		**+2.2 months**
Updated company 5 years cut-off	Weibull for both arms	-16.3 months
Updated company 6 years cut-off	Weibull for both arms	-13.7 months
Updated company 7 years cut-off	Weibull for both arms	-11.2 months

Updated company 8 years cut-off	Weibull for both arms	-8.9 months
Updated company 14 years cut-off	Weibull for both arms	-0.6 months
ERG preferred base case 5 years cut-off	Gompertz for both arms	-8.3 months
ERG preferred base case 6 years cut-off	Gompertz for both arms	-5.6 months
ERG preferred base case 7 years cut-off	Gompertz for both arms	-3.1 months
ERG preferred base case 8 years cut-off	Gompertz for both arms	-0.9 months
Key: MFS, metastatic free survival; ADT, androgen deprivation therapy; ICER, incremental cost-effectiveness ratio; ERG, evidence review group.		

In the company base case, there are only 2.22 more months in the mCRPC health state for the darolutamide+ADT arm than the ADT arm. If we assumed that time in the mCRPC health state would be greater for ADT patients, any cut-offs for darolutamide+ADT survival benefit up to 14 years met this criterion. However, when using the ERG preferred assumptions for MFS extrapolation, any cut-offs up to 8 years met this criterion. Based on the clinicians advice, it is evident that a 5 year cut-off is overly conservative and lacks face validity as no treatment in the mCRPC state has demonstrated such a large impact on survival (i.e. >8 months benefit).[1,2] Although survival in the metastatic state is not expected to be impacted, clinical experts suggested that in a conservative scenario which indeed assumes survival in the metastatic state would be negatively impacted after progression on darolutamide, the decrease in survival should not be higher than 3-4 months. This is equivalent to a threshold in the model at 7 years and 11 years in the updated company model and the one using ERG's preferred assumption on MFS respectively.[2]

The above calculations use the modelled LYs, without adjustment for the proportion of patients who progress to mCRPC. In the company base case, this proportion is estimated using the proportion of patients alive at mean MFS. Using this estimation, more patients in the ADT arm make it to mCRPC alive than darolutamide + ADT patients (as mean MFS is longer for darolutamide). However, this estimate is uncertain, and made within the limitations of the partitioned survival model. Examining pre-metastatic progression survival from the ARAMIS Sept 2018 data cut displayed in Figure 4, it may be the case that more patients on ADT alone die before progression than those on darolutamide. Therefore, for reporting the estimate of time spent in mCRPC states, the company does not believe it is appropriate to adjust for the proportion of patients reaching mCRPC, and instead assume that it is equal between arms.

Figure 4: Pre-metastatic survival for the darolutamide + ADT and ADT arms, September 2018 data-cut

Based on the evidence presented above, the company considers that a 5 years cut-off is overly conservative, and not plausible according to clinical opinion. A 11 to 14 or a 7 to 8 years cut-off

	is more realistic, depending on whether the company base case assumptions or ERG's assumptions regarding the MFS extrapolation are being used. At these cut-off ranges, the assumed negative impact on the survival of patients following progression on darolutamide + ADT as a result of removing enzalutamide and potentially abiraterone as a subsequent treatment option is more aligned with the most conservative scenario suggested by experts and with the face validity of the evidence on the benefit of the respective displaced treatments in the metastatic setting (i.e. 3-4 months).[8-10] However, this conservative scenario does not take into account the impact on the subsequent progression of the metastatic disease when having early efficacious treatment and the fact that relatively more patients could potentially benefit from other effective treatment options (such as docetaxel, cabazitaxel, radium-223, re-challenge with docetaxel etc.) as early as metastases develop and before their performance status deteriorates. Therefore, the company believes, and it was also suggested by clinical experts, that survival once patients reach metastases is unlikely to be impacted in practice.
Issue 9: Innovation/ benefits not captured in model	
Is the clinical effect seen in ARAMIS (prolonging median survival without metastases from 18 to 40 months) a step-change in the management of non-metastatic hormone-relapsed prostate cancer?	All clinical experts that were consulted in the advisory boards suggested that delaying the onset of metastases while maintaining a good tolerability and quality of life are very important therapeutic goals for the management of non-metastatic hormone-relapsed prostate cancer from both a clinical perspective as well as patient perspective, thus representing a step-change in therapy.
How does the anxiety of anticipating progression to metastatic disease affect quality of life? Would being in a clinical trial in which you could be having a new treatment relieve this anxiety? How would knowing that darolutamide may delay this disease progression affect quality of life?	Clinical experts consulted reported lack of treatment-related anxiety as a real source of concerns for their patients. It is reasonable to assume that having early treatment with darolutamide, which has been demonstrated to be efficacious at delaying metastases and prolonging life while offering a favourable tolerability, can have a significant impact on patients' quality of life as opposed to not having access to any effective treatments and having to wait for a confirmed metastasis (with the associated psychological impact) in order to receive similar treatments at a point where they may not be as efficacious as with earlier use. This treatment-related anxiety is not well captured within a clinical trial setting as it can be heavily confounded by the blinded nature of the trial.

	Additionally, there are other aspects that typically cannot be well captured within traditional cost-effectiveness frameworks, but which can nonetheless have an important impact on patients' quality of life as well as health resource utilisation. These include: - The favourable drug-on-drug interaction profile of darolutamide: allowing to maximise the target population that can be eligible for benefiting from an efficacious treatment and reducing the associated AEs and their burden on quality of life and healthcare resource utilisation - AEs linked to the metastatic disease and associated treatments

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Appendix O: New proposed PAS price results for the updated company base case and using ERG's preferred assumptions

The company would like to offer an increased PAS for darolutamide of [redacted] ahead of the ACM. This is equivalent to a net price for darolutamide of [redacted]. Updated results using this new proposed PAS for both the updated company base case (as per the response to the technical report i.e. alternative scenario 3 detailed in the response to issue 5) and using ERG's preferred assumptions are presented in tables 1 and 2 below. The cost-effectiveness model version 3.0, submitted with the response to the technical report, has been used to derive these results.

Table 1: Updated company base case (as per company response to the technical report) results for darolutamide (with PAS) + ADT versus ADT (list price)

Technologies	Total costs (£)	Total LYG	Total MFS LYs	Total PPS LYs	Total QALYs	Incremental costs (£)	Incremental MFS LYs	Incremental PPS LYs	Incremental QALYs	ICER (£/QALY)
ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]					
Darolutamide + ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£10,504	1.81	-0.15	1.22	Darolutamide dominant

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.

Table 2: Updated model results using ERG's preferred assumptions (as detailed in section 6.3 of the ERG report) for darolutamide (with PAS) + ADT versus ADT (list price)

Technologies	Total costs (£)	Total LYG	Total MFS LYs	Total PPS LYs	Total QALYs	Incremental costs (£)	Incremental MFS LYs	Incremental PPS LYs	Incremental QALYs	ICER (£/QALY)
ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]					
Darolutamide + ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£12,860	1.29	-0.67	0.52	Darolutamide dominant

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.

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Technical engagement response form

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

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Your name	**Professor Amit Bahl**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Bristol Haematology and Oncology Centre, University Hospitals Bristol and Weston NHS Trust**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No disclosures in relation to tobacco industry**

Questions for engagement

Issue 1: Treatment pathway	
Is the company's assessment of the current treatment pathway and likely treatment pathway if darolutamide is available reasonable? (see table p11 technical report) In particular, after having darolutamide for non-metastatic disease is it likely that: • no one is offered enzalutamide for metastatic disease • fewer people than currently are offered abiraterone for metastatic disease • more people than currently are offered docetaxel for metastatic disease?	**Yes, it is reasonable.** Unlikely to use Enzalutamide or Abiraterone after Darolutamide as likely to be significant cross resistance. The option of Docetaxel chemotherapy would become more important after progression on Darolutamide so likely that more people than currently would be offered Docetaxel for metastatic disease.
Why would enzalutamide and abiraterone not be used after darolutamide?	**As likely to have significant cross-resistance so unlikely to have any clinically meaningful benefit to give Enzalutamide or Abiraterone after Darolutamide.**
Issue 2: Generalisability of ARAMIS to UK practice	
The table on p12 of the technical report shows the subsequent treatments in ARAMIS and those modelled by the company, which the company suggests reflects likely NHS practice. • Are abiraterone or enzalutamide taken after darolutamide expected to be effective compared with docetaxel or with best supportive care? Would these treatments be	**It is highly unlikely that Abiraterone or Enzalutamide would be offered after Darolutamide. Docetaxel likely to be more effective than Abiraterone or Enzalutamide after Darolutamide.** Generally survival figures in clinical trials (including those in control arm) are better than real-life data due to several reasons (regular monitoring, subsequent treatment, fitness of patients entering clinical trials etc). Therefore, it would be difficult to justify the statement that overall survival estimates from ARAMIS likely to underestimate survival for ADT alone because fewer people had Abiraterone or Enzalutamide after ADT alone than is seen in NHS linical practice.

offered after darolutamide in NHS clinical practice? • Are overall survival estimates from ARAMIS likely to underestimate survival for ADT alone because fewer people had abiraterone or enzalutamide after ADT alone than is seen in NHS clinical practice?	
Issue 3: Maturity of overall survival data	
Are there any long-term data for survival in people who had darolutamide + ADT or ADT alone for non-metastatic hormone-relapsed prostate cancer?	**Not to my knowledge as the only data available is from the ARAMIS study**
Issue 4: Clinical trial data used in the model	
Would most people continue darolutamide until their cancer metastasised?	Yes, provided no unacceptable toxicity and patient complying to treatment.
In absence of metastasis-free survival data from the November 2019 data cut, is the ERG approach of using a Gompertz curve to align metastasis-free survival with time on darolutamide treatment appropriate?	The surrogate to be considered is time to next systemic anti-cancer treatment as that is likely to reflect clinical practice better.
Company please provide metastasis free survival from the November 2019 data cut if available.	
Issue 5: Approach to modelling time on subsequent treatments after disease metastasis	
Company please provide a scenario in which consistent durations on 1st, 2nd and 3rd treatments for metastatic prostate cancer are used when applying weighted costs and utility values in the model	

Issue 6: Monitoring costs	
Which monitoring assumptions better reflect NHS clinical practice, the company's or the ERG's? (see table p13 technical report)	It is unlikely that NMCRPC patients would require community nurse visits and scans regularly. So the Company's monitoring assumptions are better than ERG.
What is the cost of a consultant-led outpatient appointment: £194 (ERG estimate) or £109 (company estimate)?	New Patient appointment £175 and Follow-uo appointment £80. Therefore, company estimate of £109 would be more appropriate overall.
Issue 7: Plausibility of company modelled outcomes: extrapolation of overall survival estimates from trial data	
Are there any data to validate the company's long-term overall survival extrapolations?	This is based on clinical plausibility. Unlikely to have any data to validate this in this evolving field.
Would you expect any people to be alive 20 years after diagnosis with non-metastatic hormone-relapsed prostate cancer?	Yes
Issue 8: Plausibility of company modelled outcomes: time in metastatic health state	
Is it plausible that the survival benefit in the metastatic health state would be longer after darolutamide + ADT than ADT alone? Is there a treatment benefit after stopping darolutamide?	Overall survival from start of Darolutamide will be longer. It is feasible that the survival in the metastatic state after Darolutamide+ADT will be shorter than the survival in the metastatic state after ADT alone. But as mentioned the overall survival would be longer with Darolutamide plus ADT.
Given that there may be more treatment options available after ADT alone, would it be expected that survival with metastatic prostate cancer is longer after ADT alone after than after darolutamide + ADT?	Yes, but this does not imply that the overall survival from start of NMCRPC to death would be longer. On the contrary, the overall survival would be less when taken from start of NMCRPC to death despite the survival after developing metastases potentially being longer. It is also important to consider that the health state in NMCRPC setting is better than in the metastatic state.

Are the ERG's scenarios appropriate for addressing uncertainty? Would there be no relative survival benefit with darolutamide + ADT over ADT alone after 5 years?	This is difficult to comprehend as there is likely to be a relative survival benefit with Darolutamide + ADT over ADT alone after 5 years.
Issue 9: Innovation/ benefits not captured in model	
Is the clinical effect seen in ARAMIS (prolonging median survival without metastases from 18 to 40 months) a step-change in the management of non-metastatic hormone-relapsed prostate cancer?	Yes. Spending more time in non-metastatic health state is better than spending time in metastatic state.
How does the anxiety of anticipating progression to metastatic disease affect quality of life? Would being in a clinical trial in which you could be having a new treatment relieve this anxiety? How would knowing that darolutamide may delay this disease progression affect quality of life?	QOL is a omplex issue. Some patients feel better and some feel worse in terms of anxiety in these situations. The main aspect for most of them is the control of their disease as reflected by reduction in PSA and delaying development of metastasis.

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Prostate Cancer UK**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Treatment pathway	
Is the company's assessment of the current treatment pathway and likely treatment pathway if darolutamide is available reasonable? (see table p11 technical report) In particular, after having darolutamide for non-metastatic disease is it likely that: • no one is offered enzalutamide for metastatic disease • fewer people than currently are offered abiraterone for metastatic disease • more people than currently are offered docetaxel for metastatic disease?	There is a lack of evidence for the optimal treatment sequencing subsequent to darolutamide. However, based on evidence from trials with novel anti-androgens similar to darolutamide some points can be inferred about the treatment pathway as assessed by the company. Specifically, trials with enzalutamide which shares a very similar mechanism of action, as well as abiraterone which shares some similarities to darolutamide, can be of use. Firstly, the company's assessment of the pathway after darolutamide suggests that there will be a significant increase in the number of patients receiving docetaxel. In a study looking at abiraterone before chemotherapy[1], 57% of patients received docetaxel, which is similar to the lower estimate of the number of patients who might receive docetaxel after darolutamide. In this study, the median overall survival was significantly longer in the abiraterone acetate group than in the placebo group (34·7 months [95% CI 32·7–36·8] vs 30·3 months [28·7–33·3]; hazard ratio 0·81 [95% CI 0·70–0·93]; p=0·0033). This study therefore provides evidence of a benefit of a novel-anti androgen prior to chemotherapy, and supports the company's suggestion of having docetaxel after darolutamide. However, enzalutamide has more similarities in its mechanism of action to darolutamide than abiraterone. In a study looking at enzalutamide prior to chemotherapy (PREVAIL) in mCRPC[2], 32.8% of patients received docetaxel after enzalutamide. This study found there was a 29% reduction in the risk of death in the Enzalutamide group compared to placebo; hazard ratio, 0.71; 95% CI, 0.60 to 0.84; P<0.001. This similarly provides evidence of a benefit of a novel-anti androgen with a similar mechanism of action to darolutamide prior to chemotherapy, and similarly supports the company's suggestion of having docetaxel after darolutamide. Although docetaxel has a distinctly different mechanism of action, being a cytotoxic chemotherapy, this increased provision will be dependent on patients being able to tolerate docetaxel at the metastatic castrate resistant (mCRPC) stage of disease. Men at this stage of disease are more likely to be unwell and less able to tolerate docetaxel. Other than docetaxel, in the PREVAIL study previously detailed, a similar proportion of patients received abiraterone as a subsequent treatment (20.5% in total) in the enzalutamide group. This is at the upper suggested percentage of patients receiving abiraterone after darolutamide by the company. This is calculated based on the total

	percentage of patients who received enzalutamide across the three lines of treatment in the table above. This therefore may also support the companys suggestion of receiving abiraterone after darolutamide. There is also a suggested increase in radium-223 as a subsequent treatment to darolutamide, which can be considered a reasonable assumption given that the side effect profile of radium-223 is preferable to that of docetaxel. For example, In the ALSYMPYCA trial[3], no clinically meaningful differences in the frequency of grade 3 or 4 adverse events were observed between the study groups. Further, some side effects experienced with docetaxel such as neutropenia are not common with radium-223. For example, Grade 3 febrile neutropenia was reported in one patient (<1%) in the radium-223 group and in one patient (<1%) in the placebo group in the same study. 4% of patients received radium-223 after abiraterone in a study looking at abiraterone prior to chemotherapy, which is lower than that proposed by the model after darolutamide. Radium-223 was not given to patients after enzalutamide in this study, or in the ARAMIS study[4]. Therefore, it is difficult to determine how any subsequent treatment effect might differ. The company's treatment pathway also suggests use of cabazitaxel as a second and third line therapy after darolutamide and docetaxel. In the CARD trial[5], the median overall survival was 13.6 months with cabazitaxel and 11.0 months with the androgen-signaling–targeted inhibitor (hazard ratio for death, 0.64; 95% CI, 0.46 to 0.89; P=0.008). This supports the company's suggestion that a greater % of men having cabazitaxel at these lines of therapy would be beneficial. However, the side effect profile of cabazitaxel is particularly harsh. In the CARD trial, a number of side effects occurred more often than with novel antindrogens. This included fatigue (in 4.0% vs. 2.4% of the patients), diarrhea (3.2% vs. no patients), peripheral neuropathy (3.2% vs. no patients), and febrile neutropenia (3.2% vs. no patients).
Why would enzalutamide and abiraterone not be used after darolutamide?	There is some evidence that suggests that resistance can develop to novel anti-androgens. Darolutamide and enzalutamide have similar mechanisms of action. Darolutamide inhibits androgen binding, androgen receptor (AR)[6]. Similarly, Enzalutamide is a potent, competitive binder of androgens at the level of the AR. It prevents the translocation of the AR from the cytoplasm to the nucleus. Within the nucleus, it inhibits AR binding to chromosomal DNA, which prevents further transcription of tumour[7].

	Resistance to enzalutamide has been reported and it has been shown that darolutamide can be effective in some with AR mutants (that have developed resistance to enzalutamide). However, it is unclear whether this might also be similar with darolutamide prior to enzalutamide and a clinical trial would be needed to establish this. The mechanism of action of abiraterone is more distinct from that of enzalutamide and darolutamide, and therefore suggests the company may be correct that some people may have a benefit of abiraterone for metastatic disease after darolutamide. However, a phase ii study[8] suggests that using a sequencing strategy of abiraterone followed by enzalutamide provides the greatest clinical benefit. It found that there was a longer time to second PSA progression for the sequence of abiraterone followed by enzalutamide rather than opposite treatment sequence. Given the similarity of the mechanism of action of darolutamide, it would be interesting to understand the impact of sequencing of abiraterone after darolutamide. Given the small numbers receiving each subsequent treatments in the ARAMIS trial, it is not possible to establish the effect of different treatments after darolutamide.
Issue 2: Generalisability of ARAMIS to UK practice	
The table on p12 of the technical report shows the subsequent treatments in ARAMIS and those modelled by the company, which the company suggests reflects likely NHS practice. • Are abiraterone or enzalutamide taken after darolutamide expected to be effective compared with docetaxel or with best supportive care? Would these treatments be offered after darolutamide in NHS clinical practice?	We believe this is best responded to by clinicians.

• Are overall survival estimates from ARAMIS likely to underestimate survival for ADT alone because fewer people had abiraterone or enzalutamide after ADT alone than is seen in NHS clinical practice?	
Issue 3: Maturity of overall survival data	
Are there any long-term data for survival in people who had darolutamide + ADT or ADT alone for non-metastatic hormone-relapsed prostate cancer?	
Issue 4: Clinical trial data used in the model	
Would most people continue darolutamide until their cancer metastasised?	This can be inferred from data in the ARAMIS trial. The ARAMIS trial reported on the number of people who discontinued treatment. It is reported that 8.9%(85) of patients stopped treatment in the darolutamide group compared to 8.7% (48) in the placebo group. As trial populations differ to real world populations, the number of patients discontinuing their treatment may differ from this. However, it is the best evidence we have and the benefit of delaying metastases likely means patients will want to stay on this treatment if possible.

In absence of metastasis-free survival data from the November 2019 data cut, is the ERG approach of using a Gompertz curve to align metastasis-free survival with time on darolutamide treatment appropriate?	
Company please provide metastasis free survival from the November 2019 data cut if available.	
Issue 5: Approach to modelling time on subsequent treatments after disease metastasis	
Company please provide a scenario in which consistent durations on 1st, 2nd and 3rd treatments for metastatic prostate cancer are used when applying weighted costs and utility values in the model	
Issue 6: Monitoring costs	
Which monitoring assumptions better reflect NHS clinical practice, the	

company's or the ERG's? (see table p13 technical report)	
What is the cost of a consultant-led outpatient appointment: £194 (ERG estimate) or £109 (company estimate)?	
Issue 7: Plausibility of company modelled outcomes: extrapolation of overall survival estimates from trial data	
Are there any data to validate the company's long-term overall survival extrapolations?	
Would you expect any people to be alive 20 years after diagnosis with non-metastatic hormone-relapsed prostate cancer?	
Issue 8: Plausibility of company modelled outcomes: time in metastatic health state	
Is it plausible that the survival benefit in the metastatic health state would be longer after darolutamide + ADT than ADT alone? Is there a treatment benefit after stopping darolutamide?	

Given that there may be more treatment options available after ADT alone, would it be expected that survival with metastatic prostate cancer is longer after ADT alone after than after darolutamide + ADT?	
Are the ERG's scenarios appropriate for addressing uncertainty? Would there be no relative survival benefit with darolutamide + ADT over ADT alone after 5 years?	
Issue 9: Innovation/ benefits not captured in model	
Is the clinical effect seen in ARAMIS (prolonging median survival without metastases from 18 to 40 months) a step-change in the management of non-metastatic hormone-relapsed prostate cancer?	The clinical effect of darolutamide as shown in the ARAMIS trial can be considered a step-change, as it introduces a treatment in an indication where previously there wasn't one. Darolutamide gives men in this disease state access to the opportunity for a delay in median survival without metastases (from 18 months to 40 months). Put simply, it means that patients can live for longer with prostate cancer that has not metastasised. This means that patients can have the potential for a better quality of life and can avoid side effects such as pain that can be associated with metastases. They also have the potential to avoid more serious side effects such as metastatic spinal cord compression, which evidence suggests can occur in 1 to 12% of patients and requires urgent care and which, if not treated, can lead to paralysis. However, Prostate Cancer UK's view is that the most important step-change to management of non-metastatic hormone relapsed prostate cancer would be the routine use of modern imaging modalities including PSMA PET-CT and whole-

	body MRI. This would better enable the visualisation of metastases that are occult that it often not possible with current standard imaging (CT and bone scan), thus resulting in a more accurate diagnosis. Further, novel imaging discovering node-positive or oligometastatic disease gives an opportunity for treatment such as radiotherapy with curative intent at this disease stage. Trial data suggests that as a result of the limited sensitivity of standard imaging techniques, it is likely that men diagnosed with non-metastatic castrate resistant prostate cancer represent a population presenting with occult or low burden metastatic castrate resistant prostate cancer. In a retrospective trial of 200 patients, 55% of patients diagnosed with high-risk nmCRPC by conventional imaging received a diagnosis of metastatic prostate cancer after staging by a PSMA-PET scan[9]. Currently, men with a rising PSA no identification of metastases on conventional imaging are left without treatment options and left in a limbo until they progress to metastatic disease and can access abiraterone or enzalutamide.
How does the anxiety of anticipating progression to metastatic disease affect quality of life? Would being in a clinical trial in which you could be having a new treatment relieve this anxiety? How would knowing that darolutamide may delay this disease progression affect quality of life?	Men with nmCRPC have a rising PSA but no metastases visible by conventional imaging tests. The nmCRPC population is a very small population and therefore the experiences of such a small group are difficult to elucidate. However, the anxiety associated with this rise in PSA at different stages of prostate cancer has been explored through qualitative analysis and is reported widely in the literature. In one interview study, men with localized prostate cancer described the PSA-tests as a lifeline and that they had a feeling of being healthy when the PSA-value was low and stable. They found that waiting for the result of the PSA test meant a period of tense waiting, with varying levels of tension related to fear of the results[10]. Further, in an interview study of men with castrate-resistant prostate cancer, it was found that men graded PSA anxiety along with fatigue as being important when grading complications and quality of life issues[11].

	From anecdotal evidence from clinicians, we are aware that men with nmCRPC experience anxiety specifically around the inevitable progression to metastatic disease along with PSA rise, and often have considerable distress. However, given the small population size and the time frame for responding to this technical report, we were not able to find a patient case study for this specific population who could provide further details of their experience of anxiety at this stage of disease. The median survival time being metastasis free for men with nnmCRPC taking darolutamide is 40 months, an increase of 22 months from 18 months with ADT alone. However, once they progress to the stage of mCRPC, patients receive a smaller overall survival benefit. For abiraterone this is median overall survival was significantly longer in the abiraterone acetate group than in the placebo group (34·7 months [95% CI 32·7–36·8] vs 30·3 months [28·7–33·3]; hazard ratio 0·81 [95% CI 0·70–0·93]; p=0·0033). Therefore, having a treatment may enable some men to better cope with anxiety of progressing to this later stage of disease.

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Technical engagement response form

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

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **6 August 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text:

'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Tackle Prostate Cancer**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**NONE**

Questions for engagement

Issue 1: Treatment pathway	
Is the company's assessment of the current treatment pathway and likely treatment pathway if darolutamide is available reasonable? (see table p11 technical report) In particular, after having darolutamide for non-metastatic disease is it likely that: • no one is offered enzalutamide for metastatic disease • fewer people than currently are offered abiraterone for metastatic disease • more people than currently are offered docetaxel for metastatic disease?	Yes. From my experience of talking with other patients, the pathways suggested would seem reasonable. There would appear to be no evidence supporting the serial use of Enzalutamide, Abiraterone or Darolutamide. From a patient's perspective, they may well understand that Abiraterone has a different mode action to Enzalutamide and thus might think it might at least be logical to prescribe Abiraterone in preference to Enzalutamide if further drug therapy is continued after Darolutamide has already been used. It is most likely that patients would be offered Docetaxel for metastatic disease as the next treatment after Darolutamide.
Why would enzalutamide and abiraterone not be used after darolutamide?	
Issue 2: Generalisability of ARAMIS to UK practice	
The table on p12 of the technical report shows the subsequent treatments in ARAMIS and those modelled by the company, which the company suggests reflects likely NHS practice. • Are abiraterone or enzalutamide taken after darolutamide expected to be effective compared with docetaxel or with best supportive care? Would these treatments be offered after darolutamide in NHS clinical practice?	

• Are overall survival estimates from ARAMIS likely to underestimate survival for ADT alone because fewer people had abiraterone or enzalutamide after ADT alone than is seen in NHS clinical practice?	
Issue 3: Maturity of overall survival data	
Are there any long-term data for survival in people who had darolutamide + ADT or ADT alone for non-metastatic hormone-relapsed prostate cancer?	
Issue 4: Clinical trial data used in the model	
Would most people continue darolutamide until their cancer metastasised?	The assumption is YES. It would be logical for a drug to be continue for as long as it is effective but discontinued as soon as that positive benefit was lost.
In absence of metastasis-free survival data from the November 2019 data cut, is the ERG approach of using a Gompertz curve to align metastasis-free survival with time on darolutamide treatment appropriate?	
Company please provide metastasis free survival from the November 2019 data cut if available.	
Issue 5: Approach to modelling time on subsequent treatments after disease metastasis	
Company please provide a scenario in which consistent durations on 1st, 2nd and 3rd treatments for metastatic prostate cancer are used when applying weighted costs and utility values in the model	

Issue 6: Monitoring costs	
Which monitoring assumptions better reflect NHS clinical practice, the company's or the ERG's? (see table p13 technical report)	The experience of talking with patients reveals great differences in monitoring practice from one hospital to another. Much will depend on the availability of local resources – both staff and facilities for special investigations. Not every visit will automatically be with a consultant – many will be with a specialist nurse who can then refer on to the consultant if deemed necessary. Not all consultations are face to face. Some are becoming video or telephone consultations. The Covid crisis has accelerated change and this approach is likely to continue and mould the style of many consultations for the foreseeable future. Cost implications of this are unclear. The ERG assumption that a CT scan every 12 weeks is inaccurate and certainly does not reflect patient experience.
What is the cost of a consultant-led outpatient appointment: £194 (ERG estimate) or £109 (company estimate)?	
Issue 7: Plausibility of company modelled outcomes: extrapolation of overall survival estimates from trial data	
Are there any data to validate the company's long-term overall survival extrapolations?	
Would you expect any people to be alive 20 years after diagnosis with non-metastatic hormone-relapsed prostate cancer?	This would depend on not only on the aggressiveness and ultimate progress of the prostate cancer but also on other co-existing medical conditions. In addition, the older the patient at the time of diagnosis then the less likely a 20-year survival would be.
Issue 8: Plausibility of company modelled outcomes: time in metastatic health state	
Is it plausible that the survival benefit in the metastatic health state would be longer after darolutamide + ADT than ADT alone? Is there a treatment benefit after stopping darolutamide?	Many patients will, during the metastatic phase, have had periods of anxiety and distress, particularly prior to getting results of serial PSA tests to assess progress of disease. The knowledge that are being given an active and potentially effective treatment will undoubtedly reduce this. The continuation of ADT as a sole treatment is merely reinforcing the fact that the patient could be receiving sub-optimal therapy. Stopping Darolutamide would only be a logical

	and reasonable choice when the drug ceased to be effective. Survival benefit to patients taking Darolutamide could be both physiological and psychological.
Given that there may be more treatment options available after ADT alone, would it be expected that survival with metastatic prostate cancer is longer after ADT alone after than after darolutamide + ADT?	The majority of patients will tend to focus on the present. They will be more concerned with their current state of health and quality of life in the shorter term rather than the long term. It is highly unlikely that they will even consider the potential future treatments available when and if their current treatment should fail. They will be heavily influenced by their clinicians whom they expect to have the knowledge and experience to decide the best course of action for them. If Darolutamide is used earlier in the options for treatment, it effectively only removes one line of further treatment – i.e. Enzalutamide / Abiraterone. Chemotherapy and Radium 223 will still be potentially available to them. Newer treatments for advanced prostate cancer are under development / appraisal: e.g. Lutetium[177] Olaparib. The availability and uptake of advanced treatments already approved for use is likely to increase over time and the ongoing evolution of newer therapies will undoubtedly continue. Both will provide better options for patients in the advanced stages of the disease in the future.
Are the ERG's scenarios appropriate for addressing uncertainty? Would there be no relative survival benefit with darolutamide + ADT over ADT alone after 5 years?	
Issue 9: Innovation/ benefits not captured in model	
Is the clinical effect seen in ARAMIS (prolonging median survival without metastases from 18 to 40 months) a step-change in the management of non-metastatic hormone-relapsed prostate cancer?	This is undoubtedly a major step forward in the management of non-metastatic hormone relapsed prostate cancer. Currently patients (and their clinicians) have no approved treatment pathway available in this clinical situation. Establishing a clearly denoted pathway to provide an active management strategy is certainly a step-change from the currently passive state of therapy which is basically doing nothing until metastases are identified. It could be argued that the drug or class of drugs under review may not necessarily be new or innovative, but the change in treatment policy certainly is. An extra 22 months of being progression free and with an acceptably good quality of life would be hugely beneficial to patients. Anxiety will still play a part, but less so.

	One patient said: *"It's a no-brainer. I can have treatment which will help me and hopefully extend my life. Where are the negatives in that?"*
How does the anxiety of anticipating progression to metastatic disease affect quality of life? Would being in a clinical trial in which you could be having a new treatment relieve this anxiety? How would knowing that darolutamide may delay this disease progression affect quality of life?	Anxiety is about both the unknown and the known: *"How long have I got to live" "What can be done to help me? I know my cancer is getting worse."* *"I know my time left is short. At least I still have time to make plans for myself and my wife"* Being in any clinical trial can have positive psychological benefits, but these should be similar in patients taking placebo or active drugs. Knowing a treatment may delay disease progression enables a degree of future planning, time to sort out affairs in life (a will, a power of attorney, etc if not already done), It gives hope for the future. Telling patient that no treatment is currently available does none of this. Patients do not expect miracles. Each patient is unique, and their expectations will differ. However, they have one basic, simple request: *"I'd like to live as long as I can in the best way that I can"* Again, it is succinctly described by the patient above: *"It's a no-brainer"*

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

ERG critique of the company response to the technical engagement report

Produced by Aberdeen HTA Group

Date completed: 14 August 2020

In response to the technical engagement (TE) report, the company addressed each of the points raised and submitted some revised modelling and additional evidence to support their preferred modelling assumptions.

This short commentary critiques the company's response to each of the main issues raised:

1. Treatment pathway
2. Generalisability of ARAMIS to UK practice
3. Maturity of overall survival data
4. Clinical trial data used in the model; with respect to the uncertainty around using different data cuts to inform metastasis-free survival and time on treatment and overall survival
5. Approach to modelling time on subsequent treatments after disease metastasis
6. Monitoring costs
7. Plausibility of company modelled outcomes: extrapolation of overall survival estimates from trial data
8. Plausibility of company modelled outcomes: time in metastatic health state

This commentary should be read in conjunction with the company TE response.

1. Treatment pathway

The technical engagement report sought clarity on the subsequent treatment pathway that would be used in the NHS following progression to mCRPC on darolutamide + ADT or ADT alone. It sought clarity on why enzalutamide or abiraterone would not be used, or be used minimally in the case of abiraterone, following progression on darolutamide plus ADT.

The company note in their response that they have made further efforts to validate their proposed treatment pathways in a further advisory board meeting held in July 2020 with 8 UK clinical experts (see company response for details). They note that all experts supported the modelled pathways. They further reference evidence indicating a lack of efficacy for the sequential use of enzalutamide after progression on abiraterone in mCRPC (and vice a versa), and clinical opinion suggesting that similar cross resistance is likely to be seen following progression from nmCRPC on darolutmaide - acknowledging that evidence on the sequential use of abiraterone and enzalutamide following darolutamide is lacking. They further reference clinical opinion from their July 2020 advisory board that other treatments (such as

docetaxel) are more likely to be effective following progression on darolutamide and would be used in preference to enzalutamide/abiraterone.

The ERG is satisfied with the arguments and rationale provided for the modelled treatment pathways, but their remains some uncertainty as to what the NHS England commissioning policy will be at this stage.

2. Generalisability of ARAMIS to UK practice

Related to the treatment pathway, the technical engagement report sought further consultation on whether the mismatch between subsequent treatments received in ARAMIS and those applied in the model to represent current NHS practice, is likely to limit the generalisability of the OS data from ARMIS to the UK NHS.

With respect to the observed sequential use of enzalutamide and abiraterone following progression on darolutamide in ARAMIS, the company noted the limited evidence to support an OS gain for these treatments compared to docetaxel in this context. They note that the clinical experts consulted in July 2020 suggested that these three treatments have a comparable effect on OS compared to BSC in the metastatic CRPC setting. They also note the exploratory analyses of ARAMIS overall survival data by subsequent therapy received (abiraterone, enzalutamide and docetaxel), which showed no significant difference in OS for these subsequent treatments when taken after progression on darolutamide. The company further highlight clinical expert opinion from their July 2020 advisory board, that because of likely cross resistance between darolutamide, enzalutamide, and abiraterone, "*response rates are expected to be better for docetaxel or alternative agents like radium-223 compared to enzalutamide/abiraterone if taken after progression on darolutamide, particularly in patients with aggressive phenotype disease that are expected to progress early".* Given the apparent underuse of chemotherapy and lack of radium-223 prescribing in the darolutamide arm of ARMIS, the company note that "*the overall clinical experts' opinion suggests the OS for the darolutamide arm in ARAMIS is likely to underestimate the expected survival in the UK*."

Regarding the lower use of abiraterone or enzalutamide following progression on ADT alone in ARAMIS compared to NHS clinical practice, the company suggest "*it is currently unclear whether the change in subsequent therapy use to reflect UK clinical practice for the ADT arm would drastically impact overall survival estimates*". However, the company note their clinal

expert opinion that docetaxel/enzalutamide/abiraterone all demonstrate similar improvements in OS in the mCRPC setting, and that the relatively lower use of enzalutamide/abiraterone compared to docetaxel after ADT in ARAMIS is unlikely to underestimate the OS expected in clinical practice. They further note the clinical experts' suggestion that the 170 patients who crossed-over to darolutamide during the open-label phase of ARMIS would have likely overestimated the OS of the ADT arm in ARAMIS compared to the current clinical practice. However, the company did provide scenarios that formally adjusted OS for this cross-over, which appeared to have a small impact on the unadjusted OS Kaplan Meier plot. Further, their analysis of OS by subsequent treatments following ADT, did hint towards a potential benefit for enzalutamide compared to docetaxel (acknowledging the low numbers), which could counter the generalisability issue driven by cross over from ADT to darolutamide.

Based on the above rationale, the ERG is generally satisfied that the observed OS data from the ARMIS are broadly generalizable to the UK nmCRPC population. However, uncertainties remain over the long-term extrapolation of these data (see below). The data remain immature for the purpose of informing the impact of alternative subsequent treatments on OS, and there do not appear to be any long-term data (beyond median OS) to help validate the OS extrapolations in this patient population.

3. Maturity of overall survival data

The TE report asked if there are any long-term data available for survival in people who had darolutmaide + ADT or ADT alone for nmHRPC. The company indicate that they did not identify any in their systematic literature review, and the clinical experts consulted in their July 2020 advisory board were not aware of any either. In their response, the company state that their extrapolated median OS estimates for daorlutamide + ADT (71.75 months) and ADT alone (59.79 months), are in line with the observed median estimates available from the SPARTAN and PROPSPER trials (Small et al. 2020; Sternberg et al. 2020). In the most recent analysis of the SPARTAN trial, median OS has been reported as 73.9 months for apalutamide + ADT and 52.8 months for ADT alone in a comparable nmCRPC population. In the final OS analysis of the PROSPER trial, median OS was 67 months for enzalutamide +ADT was and 56.3 months for ADT alone in a comparable patient population. However, examining the company base case model trace, the extrapolated median OS for darolutamide + ADT is 81.87 months rather than the 71.75 stated. The model in fact projects a median of

OS of 71.75 for darolutamide + ADT when mortality in the darolutamide arm is equalised to mortality in the ADT arm from 5 years, as per the ERG's original base case.

The projected medians from the company model base case are 3-7 months higher than available observed estimates for ADT alone, but approximately 8 and 15 months higher than available estimates for apalutamide and enzalutamide, respectively. This further suggests that the company's base case estimated survival benefit for darolutamide + ADT versus ADT alone may be optimistic, and concerns remain around the consistency of the longer term survival projections given the subsequent treatment pathways (discussed under issue 7 and 8 below).

4. Clinical trial data used in the model

The technical engagement report questions the company's partitioned survival model's use of different data cuts for metastasis-free survival (September 2018) and for time on treatment and overall survival (November 2019). This related to the observation that the darolutmide ToT curve shifted downwards when updated to the Nov 2019 data-cut, raising the possibility that MFS would have taken a similar downward shift had it also been updated – assuming most discontinuation events are due to metastatic progression.

In response to this issue the company have clarified that no further MFS analyses were pre-planned past the 2018 primary analysis data-cut as per the Statistical Analysis Plan of ARAMIS. Consequently, there is no updated independent metastasis assessment available for the Nov 2019 data cut. Therefore, on the advice of clinical experts, the company have looked at how the time to next antineoplastic therapy curves change between the data cuts, as a proxy for how the MFS curves might have behaved had data been available to update them (the assumption being that subsequent antineoplastic therapies are initiated following progression to metastasis). Comparison of these curves, provided in Figure 2 of the company response document, indicate that they change very little between the data cuts. However, they also seem to illustrate that, in the context of ARMIS, time to subsequent antineoplastic therapy is not a particularly good proxy for MFS, the curves being substantially higher and flatter than the corresponding MFS curves, reflecting the relatively low proportion of progressed patients who appear to have initiated a further therapy by the time of the data cut-offs.

The company further criticise the ERG's approach of relying on the more pessimistic Gompertz projection of Sept 2018 MFS in the absence of Nov 2019 MFS data. They highlight the poor statistical fit of the Gompertz curve to the observed Sept 2018 MFS data. The ERG acknowledges this but note that it was selected for greater consistency with the updated Nov 2019 ToT curve selection, not for statistical fit with the observed 2018 MFS data. The company also note that their clinical experts said it lacked clinical validity, "*projecting that 0% of patients will be in the metastatic free state at 5 years*". However, this is not in fact the case, with the Gompertz curves still projecting that approximately 21% remain metastasis free at 5 years on darolutmaide plus ADT, and 2% remain metastasis free on ADT alone. It is therefore not clear to the ERG what the clinical experts were referring to when making this observation.

Given the lack of Nov 2019 MFS data for comparison, and the limitations of the proxy suggested by the company, the ERG believe it is not possible to conclude with confidence what the darolutamide MFS curve should look like in relation to the Nov 2019 ToT curve. If indeed the observed ToT falls so far below MFS during the observed phase, this may also raise a question regarding the future shape of the extrapolated MFS curve.

The ERG acknowledges the uncertainty and suggest that their chosen Gompertz curve may offer a lower limit for the MFS extrapolation. However, the ERG also note the uncertainty surrounding the extrapolation of the darolutamide ToT curve itself, and suggest that the Weibull ToT curve for darolutamide also represents a relevant scenario.

5. Approach to modelling time on subsequent treatments after disease metastasis

There was an inconsistency in the company's model (submitted in response to the clarification letter), with respect to different state durations being assumed for the mCRPC substates (PD1-PD3) for the purpose of estimating weighted mCRPC utility values and for estimating proportions transitioning to the subsequent PD substates for subsequent treatment costs. The utility value calculations were weighted by the expected life-years in mCRPC sub-states obtained from the reported model output of TA377, whilst the latter relied on median estimates of time on subsequent treatments, which will tend to overestimate the speed of transition through the mCRPC substates but underestimate expected treatment costs within the substates. The technical engagement report therefore requested that the company conduct a scenario analysis which assumed consistent durations in these progressive disease (PD)

substates for both purposes, and which used estimates of mean times on subsequent treatments rather than medians where possible. The ERG further clarified during the technical engagement call, that mean times on subsequent treatments should ideally be reflective of the treatment line they are used at; e.g. mean times on enzalutamide and abiraterone are expected to be shorter when used at PD2 and PD3 compared to PD1.

The company have addressed this in their response to the technical engagement report and have offered three scenarios for approximating times in state for the purpose of weighted utility calculations and expected proportions progressing through to each mCRPC substate. They have also shown the impact of applying each of these with median and mean subsequent treatment durations for the costing of each subsequent therapy (see Table 2 of the company response document). The company prefer their third approach as detailed in their TE response document. This approach essentially uses estimated progression free survival for each subsequent treatment in the mCRPC health state to model the expected durations in each PD substate. The means are estimated using reported median PFS while assuming exponential distributions. These durations are then used in the utility and the cost calculations; with the cost calculations appropriately using separate time on treatment estimates. As indicated, the costs can be based on median or mean times on treatment, where means are again approximated from reported medians assuming exponential distributions for ToT. The ERG is generally satisfied that this approach offers an improvement on the company's previous approach and support the use of mean rather than median times on subsequent treatment for costing purposes. This improves the cost-effectiveness of darolutamide. There is the caveat, however, that the applied estimates of PFS and times on subsequent treatments reflect expected durations when given in mCRPC PD1. In line with published literature, it is expected that treatment durations for enzalutamide and abiraterone may be shorter when provided at PD2 or PD3, after docetaxel. The ERG has therefore assessed the impact of altering the state durations and one-off costs for these drugs when given in PD2 and PD3. This relies on reported median PFS from the AFFIRM trial of enzalutamide (Scher et al., 2012) and the COU-AA-301 trial of abiraterone (Fizazi et al, 2012). These trials relate to the use of enzalutamide and abiraterone after docetaxel in the mCRPC setting. Reported median PFS is 8.3 months and 7.4 months for enzalutamide and abiraterone respectively, giving expected mean durations of 11.97 and 10.68 months based on exponential extrapolations. These durations were used as expected times to progression and

time on treatment for enzalutamide and abiraterone in PD2 and PD3 in the ERG's revised approach.

A further issue with the company revised base case is that time in the metastatic substates (PD1-3) for those receiving best standard care (ADT alone), is taken as an average of estimated progression free survival for the active mCRPC treatments. The ERG believes that this will likely overestimate time to progression in those receiving BSC, and that this should instead be based on time to progression with ADT alone as observed in the PREVAIL trial (Beer et al. 2014). The company provided this as a scenario in Table 3 of their response document.

6. Monitoring costs

The company provide further support from clinical experts consulted during the July 2020 advisory board for their chosen monitoring resource use estimates as outlined in their response document. The ERG do not have a strong preference with respect to the monitoring resource use applied, but on balance prefer the modified resource use estimates from TA580 on the advice of their own clinical expert who felt that the frequency of CT scanning looked substantially too low in the company's base case for a contemporary cohort with high-risk nmCRPC, who he believed would be monitored more closely for progression. The frequency of CT scans in the company base case appeared to be only about once every 5.5 years in the nmCRPC state, and once every 1.36 years in the mCRPC state. With respect to the unit costs for monitoring visits, the ERG retains a preference for the more specific unit cost of oncology outpatient attendance.

7. Plausibility of company modelled outcomes: extrapolation of overall survival estimates from the trial data

The TE report sought further consultation on the company's OS survival curves used in the model, by asking if there are any available external data to help validate the survival outcomes for darolutamide + ADT or ADT alone. As indicated above under issue 3, the company have compared their extrapolations of median OS for each arm against observed medians from the SPARTAN and PROPSER trials, of apalutamide + ADT versus ADT alone and enzalutamide + ADT versus ADT alone, respectively. However, as indicated above, the company appear to have misread their median OS projection in the darolutamide arm of the

model, which at 81.87 months is in fact higher than observed median OS for apalutamide (73.9 months) or enzalutamide (67 months).

The ERGs clinical advisor was off he opinion that the Weibull extrapolation of OS in the darolutmaide arm of the company model looked overly optimistic and did not expect to see any patients with high risk nmCRPC surviving to 20 years. The company further consulted eight clinical experts on this matter during their July 2020 advisory board meeting, who they note considered "*it possible that a small proportion of patients treated with darolutamide would survive ~20 years in clinical practice*". This, the company note, is reflected in their base case extrapolation, with 2.35% and 0.02% of patients surviving to 20 years in the darolutamide+ADT and ADT arms, respectively. The ERG believes this remains an area of uncertainty and have remaining concerns about the implied relative OS benefit for darolutamide lasting throughout the time horizon of the model (see issue 8).

8. Plausibility of company modelled outcomes: time in metastatic health state

The TE report sought further consultation on issues relating to the plausibility of the company's projections of expected survival in the mCRPC state in the alternative arms of the model. The ERG believed that those receiving ADT alone in the nmCRPC state would be expected to accumulate greater life years in mCRPC state compared to those who receive darolutmaide + ADT in the nmCRPC state. This is for two reasons: 1) people progress to the mCRPC quicker and earlier in the ADT arm, meaning a greater proportion of patients will make the transition in the first place (i.e. fewer will die of other causes prior to progression); and 2) once in the mCRPC health state, patients in the ADT arm have access to a greater number of life extending treatment options, as reflected in the stream of subsequent treatment costs modelled. The ERG therefore suggested in their report that conditional on progression to mCRPC, ongoing survival would be greater per progressed patient in the ADT arm than in the darolutmaide arm. This would hold unless treatment with darolutamide in the nmCRPC health state confers a relative survival benefit that lasts beyond progression into the mCRPC state, when darolutamide treatment would be discontinued.

The company consulted their 8 clinical experts on this issue in their July 2020 advisory board meeting. The clinical experts stated that the "*focus of treatment efficacy should be on how long patients are asymptomatic as early efficacious treatments can affect the subsequent aggressiveness and progression of the metastatic disease and therefore post-progression*

survival". This suggests that it may be plausible for patients to progress more slowly from the point of progression to the mCRPC state on darolutamide, despite having fewer subsequent treatments following progression. Nevertheless, post hoc analysis performed by the company looking at post-progression survival by initial treatment allocation in ARMIS did not provide evidence to support longer post-progression survival in the darolutmide arm (see Figure 3 of the company's response to technical engagement), as the company's original and revised base cases suggest. The company suggest that the lack of significant difference in the post-progression survival favoring darolutamide in ARAMIS is likely due to post-progression survival in the ADT arm being confounded by the 170 patients crossing over and receiving darolutamide before progression. However, post-progression survival in the ADT arm of ARAMIS may also be underestimated by the lower than expected (and modelled) proportion of patients receiving subsequent treatment with abiraterone or enzalutamide. The ERG believes the expected duration of post progression survival remains an area of uncertainty, requiring scenario analysis to illustrate the impact of a range of possible assumptions.

The clinical experts consulted by the company suggested that "*in a conservative scenario which indeed assumes survival in the metastatic state would be negatively impacted after progression on darolutamide, the decrease in survival should not be higher than 3-4 months".* The company have implemented this by equalising mortality from future time points and highlighting the cut-offs that lead to a 3-4 month deficit in mCRPC life years in the darolutamide arm using the company's preferred MFS extrapolation and the ERGs original base case MFS extrapolation (see Table 4 of the company response document). This shows that a cut-off at 11-14 years or 7-8 years, respectively, achieves a life year deficit of <4 months as suggested by the clinical experts. However, the ERG do not believe these scenarios to be overly conservative as they do not adjust for the proportion of patients who would transition to mCRPC in the respective arms of the model; i.e. over the duration of the model, more patients in the ADT arm would be expected to make it to the mCRPC state as they progress more quickly at a younger age. i.e. the difference in post-progression survival (per progressed patient) would likely be less than those provided in Table 4 of the company response. However, the ERG accepts that exact proportions making the transition in the context of the Part-SA model is difficult to accurately estimate. Table 1 below provides the ICER for each cut-off scenario explored by the company in Table 4 of their response, as these were not provided in their submitted response document.

Table 1 Cost-effectiveness results of survival benefit cut-off scenarios assessed by the company

Survival benefit cut-off	**Assumption for MFS extrapolation**	**PPS survival difference (months): darolutamide+ADT vs ADT** *(Daro-ADT)*	**Total costs**		**Incremental cost**	**Total QALYs (Lys)**		**Incremental QALY**	**ICER**
			Darolutamide	**ADT**		**Darolutamide**	**ADT**		
Updated company model base case		**+2.2 months**	[redacted]	[redacted]	**(£4,205)**	[redacted]	[redacted]	**1.22**	**Darolutamide dominant (-£3,433)**
Updated company 5 years cut-off	Weibull for both arms	-16.3 months	[redacted]	[redacted]	(£12,025)	[redacted]	[redacted]	0.59	Darolutamide dominant (£20,426)
Updated company 6 years cut-off	Weibull for both arms	-13.7 months	[redacted]	[redacted]	(£10,284)	[redacted]	[redacted]	0.70	Darolutamide dominant (£14,697)
Updated company 7 years cut-off	Weibull for both arms	-11.2 months	[redacted]	[redacted]	(£9,210)	[redacted]	[redacted]	0.80	Darolutamide dominant (£11,566)
Updated company 8 years cut-off	Weibull for both arms	-8.9 months	[redacted]	[redacted]	(£8,260)	[redacted]	[redacted]	0.88	Darolutamide dominant (£9,382)
Updated company 14 years cut-off	Weibull for both arms	-0.6 months	[redacted]	[redacted]	(£5,068)	[redacted]	[redacted]	1.15	Darolutamide dominant (£4,389)
ERG base case 5 years cut-off	Gompertz for both arms	-8.3 months	[redacted]	[redacted]	£3,887	[redacted]	[redacted]	0.46	£8,429
ERG base case 6 years cut-off	Gompertz for both arms	-5.6 months	[redacted]	[redacted]	£4,308	[redacted]	[redacted]	0.58	£7,431
ERG base case 7 years cut-off	Gompertz for both arms	-3.1 months	[redacted]	[redacted]	£4,695	[redacted]	[redacted]	0.69	£6,819
ERG base case 8 years cut-off	Gompertz for both arms	-0.9 months	[redacted]	[redacted]	£5,036	[redacted]	[redacted]	0.78	£6,419

Key: MFS, metastatic free survival; ADT, androgen deprivation therapy; ICER, incremental cost-effectiveness ratio; ERG, evidence review group. Cost parentheses indicate negative value (darolutamide dominant).

ERG reflection on the key modelling assumptions

Reflecting on the company's response, the ERG has the following observations on the key modelling assumptions feeding into the model:

1. The company's base case OS extrapolation remains optimistic for darolutamide, as further suggested by comparison of the extrapolated median OS against available observed median estimates for apalutamide and enzalutamide in this indication.
2. Given the data presented on post-progression survival in ARAMIS, and the higher usage of life extending subsequent treatments modelled following progression on ADT alone, the ERG believes that post-progression survival (ideally per progressed patient) should be at least no worse in the ADT arm compared to the darolutmide arm.
3. There is remaining uncertainty regarding the MFS extrapolation, driven by the unavailability of updated MFS data from the later Nov 2019 data-cut, which demonstrated a substantial increase in treatment discontinuation compared to the earlier Sept 2018 data cut. However, the ERG acknowledges that their chosen Gompertz MFS extrapolation may offer a lower limit on what is plausible.
4. In general, the ERG accepts the company's changes around modelling expected time in subsequent mCRPC substates, except for the assumed abiraterone and enzalutamide durations in PD2 and PD3. These currently reflect the duration of these treatments when given prior to docetaxel in the treatment pathway (in PD1). This also results in the sum of expected subsequent mCRPC state times in the ADT arm being longer than the overall mCRPC life years predicted by the model. Further, for the purpose of estimating time in state for those receiving BSC care in PD1-PD3, the ERG believe that this should be based on the observed median duration of treatment with ADT alone (at PD1) as observed in the PREVAIL trial (Beer et al., 2914) rather than taken as an average of times on the active treatments. The company provided this as a scenario in Table 3 of their response document.
5. The ERG do not have a strong preference with respect to the monitoring costs applied, but on balance prefer the modified resource use estimates from TA580 on the advice of their own clinical expert who felt that the frequency of CT scanning looked substantially too low in the company's base case for a contemporary cohort with high-risk nmCRPC. With respect to the unit costs for monitoring visits, the ERG retains a preference for the more specific unit cost of oncology outpatient attendance.

Based on the above, the ERG provides a revised set of analyses below. This includes a rework of Table 3 from the original ERG report, but incorporating: i) the company's revised approach (approach 3) to estimating time in the mCRPC substates; ii) the basing of subsequent treatment durations and costs on extrapolated means rather than medians; iii) the company's alternative PREVAIL trial source for estimating time in the PD substates when receiving BSC (ADT only); and iv) alternative subsequent state and treatment durations for those receiving abiraterone or enzalutamide at PD2 or PD3. These changes are shown incrementally in Table 2.

From this new reference point, we present the alternative scenarios for extrapolation of OS and ToT as per Table 3 in the original ERG report (scenarios 1-3). To further address the points raised in the TE report and the company response, we also assess the impact of restoring the Weibull curves for extrapolation of MFS as per the company preference, but with equalisation of mortality to the ADT arm from time points that ensure mCRPC life years in the ADT arm are at least no lower than those in the darolutamide arm (scenarios 4-8). We also assess the impact of pairing the MFS Weibull extrapolations with the ERG alternative OS extrapolation for darolutamide which takes the average of the Nov 2019 generalised gamma and Weibull OS curves (scenario 8). We also further assess the impact of paring the Weibull extrapolation of MFS with the Weibull extrapolation of the darolutamide 2019 ToT (scenarios 9 and 10), and alternative mortality equalization scenarios with the company preferred monitoring costs (11-13). Finally, there is some uncertainty around time on treatment with cabazitaxel in PD2 and PD3, which may be overestimated using the company abased on the definition of PFS used (de Bono et al., 2010). The TROPIC trial of Cabazitaxel reports PFS under a composite definition where progression is measured by PSA progression, tumor progression, pain progression or death (de Bono et al., 2010). The median time to progression using this definition is 2.8 months. The time on treatment proxy in the darolutamide model uses the median time to tumour progression of 8.8 months (page 34 ERG report TA391). This generates uncertainty regarding the cost in the PPS state – predominantly in the darolutamide arm. Regardless of the progression definition, the cabazitaxel treatment regimen is for a maximum of 10 (3 week long) cycles which is significantly less than the 8.8 months used for the calculation of costs in the model. The final scenarios (14-16) in Table 2 explore the impact of reducing these costs across different scenarios.

Reflecting on the company response, the ERG finds it difficult to point to a single analysis representing its preferred modelling assumptions. The most pertinent uncertainties relate to the MFS and OS extrapolations for darolutamide, the revision to the original ERG base case offering the most conservative extrapolations for both, and the scenario 4 offering the most optimistic extrapolations the ERG believes plausible given the actual observed data presented and subsequent treatment pathways modelled. Figure 1 below illustrates the range of OS extrapolations explored in the Table 2 scenarios. There are further uncertainties relating to the chosen ToT curve for darolutamide, which determines how closely it tracks to MFS, and the cost of cabazitaxel when used as a subsequent treatment. The committee should refer to the accompanying confidential appendix for all ICERs inclusive of confidential discounts on subsequent treatments.

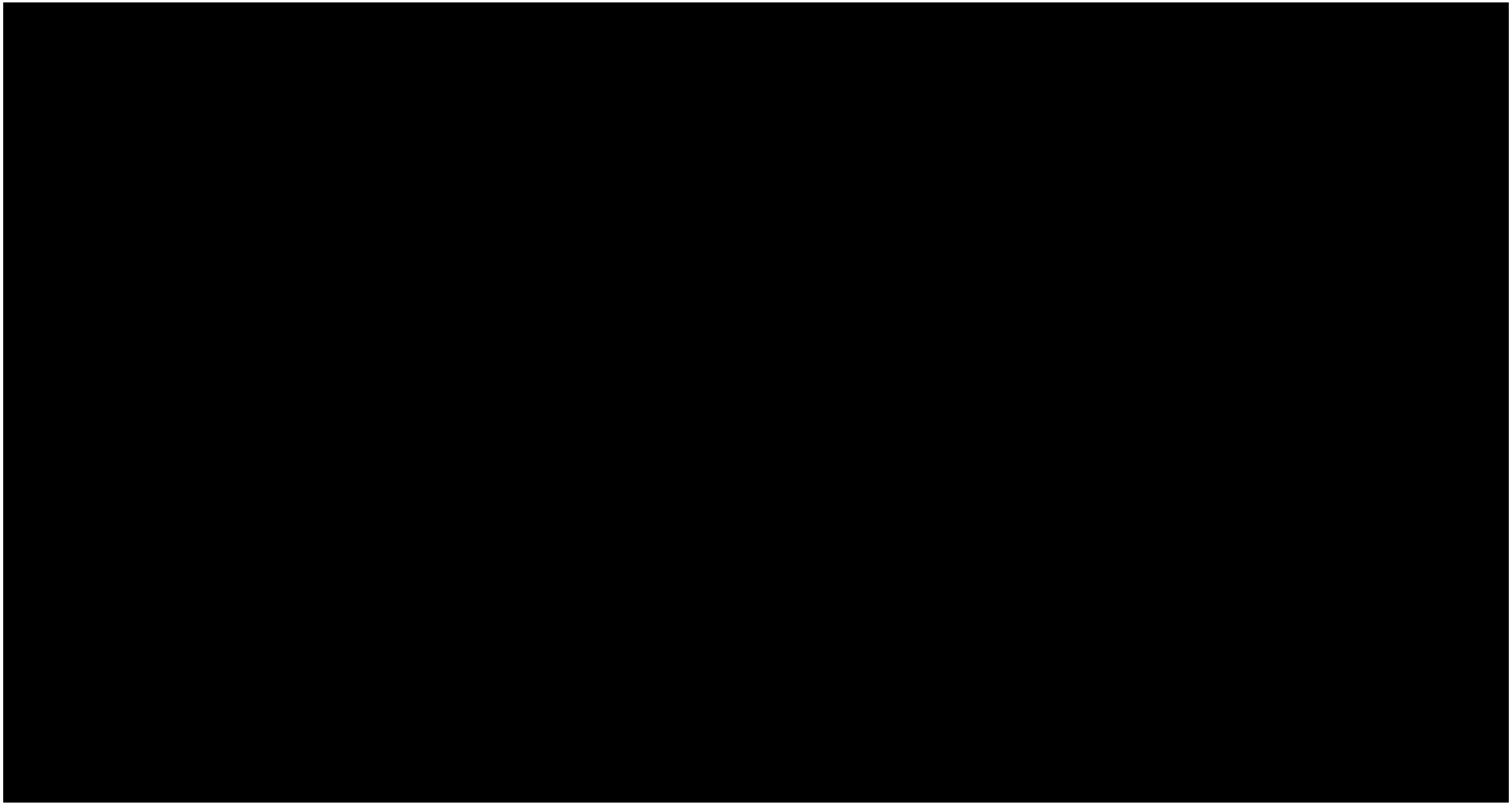
Table 2 ERG cost-effectiveness scenario analysis

Description	Darolutamide + ADT			ADT alone				mCRPC life years		
	Costs	QALY	LY	Costs	QALY	LY	ICER vs ADT	Darolutamide + ADT	ADT alone	Difference (Months)
ERG original base	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,429	[redacted]	[redacted]	-8.27
i) + Company's revised approach to PD state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9,786	[redacted]	[redacted]	-8.27
ii) + subsequent treatment durations based on extrapolated means	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(£12,583)	[redacted]	[redacted]	-8.27
iii) + PREVAIL source for estimating time in PD states for BSC (ADT only)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(£12,279)	[redacted]	[redacted]	-8.27
iv) + alternative subsequent state and treatment durations for those receiving abiraterone or enzalutamide at PD2 and PD3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(£9,863)	[redacted]	[redacted]	-8.27
Revised ERG original base case incorporating i-iv above	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(£9,863)	[redacted]	[redacted]	-8.27
1. Equalise mortality to ADT arm from 7 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(£5,532)	[redacted]	[redacted]	-3.14
2. Average of Nov 2019 generalised gamma and Weibull for darolutamide OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(£4,812)	[redacted]	[redacted]	0.11
3. Weibull extrapolation of Nov 2019 darolutamide ToT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(£4,825)	[redacted]	[redacted]	-8.17
4. Weibull extrapolation of MFS but with equalisation of mortality from 11 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(£4,880)	[redacted]	[redacted]	-3.68
5. Weibull extrapolation of MFS but with equalisation of mortality from 12 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(£4,547)	[redacted]	[redacted]	-2.43

6. Weibull extrapolation of MFS but with equalisation of mortality from 13 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(£4,298)	[redacted]	[redacted]	-1.41
7. Weibull extrapolation of MFS but with equalisation of mortality from 14 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(£4,113)	[redacted]	[redacted]	-0.57
8. Weibull extrapolation of MFS but with OS taken as the average of Nov 2019 generalised gamma and Weibull OS extrapolations for darolutamide.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(£7,389)	[redacted]	[redacted]	-7.95
9. Weibull extrapolation of MFS but with equalisation of mortality from 11 years and Weibull extrapolation of darolutamide 2019 ToT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(£2,227)	[redacted]	[redacted]	8.85
10. Weibull extrapolation of MFS but with OS taken as the average of of Nov 2019 generalised gamma and Weibull OS extrapolations for darolutamide, and Weibull extrapolation of darolutamide 2019 ToT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(£4,177)	[redacted]	[redacted]	-7.95
11. Revised ERG original base case + company preferred monitoring assumptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(£12,772)	[redacted]	[redacted]	-8.27
12. Scenario 1 + company preferred monitoring assumptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(£5,517)	[redacted]	[redacted]	-3.14
13. Scenario 4 + company preferred monitoring assumptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(£4,625)	[redacted]	[redacted]	-3.68
14. Revised ERG original base case + TROPIC based definition of PFS for cabazitaxel treatment duration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(£18,437)	[redacted]	[redacted]	-8.27

15. Scenario 1 + TROPIC based definition of PFS for cabazitaxel treatment duration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(£11,780)	[redacted]	[redacted]	-3.14
16. Scenario 4 + TROPIC based definition of PFS for cabazitaxel treatment duration.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(£8,048)	[redacted]	[redacted]	-3.68

Figure 1: OS curves for alternative scenarios explored in Table 2



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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

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

This document is the technical report for this appraisal. It has been prepared by the NICE technical team.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

1 Key issues summary

Issue	Summary	Technical Team Preliminary Judgement
Treatment pathway *It is unclear which treatments people would have after darolutamide + ADT (androgen deprivation therapy) in clinical practice.* ***Why is this an issue?*** *The treatments people have after darolutamide + ADT and ADT alone will affect the estimated survival and total costs of darolutamide + ADT compared with ADT alone*	Company: • notes darolutamide has a different mechanism of action to other 'second generation androgen receptor inhibitors' (that is, enzalutamide and apalutamide). • considers that after the cancer metastasises: 1) enzalutamide would not be offered after darolutamide, 2) fewer people would have abiraterone after darolutamide than after ADT alone 3) more people would have docetaxel after darolutamide than after ADT alone. (see Figure 3 Document B, company submission) This was based on a survey of UK oncologists. • Evidence Review Group (ERG) agrees with company statements.	• Enzalutamide is not recommended for non-metastatic hormone-relapsed prostate cancer (TA580); an appraisal of apalutamide for this indication is currently in development. • There are no guidelines on whether clinicians should offer enzalutamide or abiraterone after darolutamide once a person's prostate cancer has metastasised. Currently abiraterone or enzalutamide can only be offered once in the NHS treatment pathway. • The company's assumptions on how the treatment pathway will change if darolutamide is available need to be validated. **What additional information at engagement would help address the issue?** • Clinical expert clarification on the treatment pathway. • NHS England comments on likely commissioning policy.
Generalisability of ARAMIS trial to NHS *ARAMIS results may not be generalisable to NHS because of the subsequent*	• There are differences between the treatments people had after disease metastasis in ARAMIS and those the company suggests will constitute NHS practice and modelled by the company. • The ERG clinical expert stated that in ARAMIS, after ADT alone, the proportion of patients having	• If the treatments after darolutamide + ADT or ADT alone differ from those used in the NHS this could bias the survival estimates from ARAMIS. • It needs to be determined:

Issue	Summary	Technical Team Preliminary Judgement
treatments patients had after their cancer metastasised ***Why is this an issue?*** *This may bias the overall survival estimates for darolutamide + ADT vs. ADT alone if patients had less access to life-extending treatments after ADT than they would in UK clinical practice.*	docetaxel appears higher, and the proportion having abiraterone or enzalutamide appears lower than in NHS clinical practice (tables 8 and 12 ERG report). Also, some people in ARAMIS had enzalutamide after darolutamide + ADT, which would not be expected in clinical practice. • ERG suggest this may bias overall survival results in favour of darolutamide. This is because fewer people had the life-extending treatments enzalutamide or abiraterone after ADT alone in ARAMIS than would in clinical practice, so the survival on ADT alone may be underestimated in ARAMIS. • ERG noted that only half of patients that stopped the darolutamide + ADT had a subsequent treatment. • Company notes in the factual accuracy response to the ERG report that some patients in ADT arm switched to darolutamide after unblinding (n=[redacted]), so estimated relative survival benefit of darolutamide + ADT may be conservative. Company presents ADT alone curve adjusted for switching using 2 methods, but uses unadjusted data in base case noting adjustment had only a small effect but introduces uncertainty. • Company also notes that radium-223 is a life-extending treatment that could be taken after darolutamide but was not available in ARAMIS. This may potentially underestimate survival expected with darolutamide in clinical practice. • Company provided post-hoc Kaplan-Meier plots from the point of initiating subsequent treatments for darolutamide + ADT and ADT alone. Company suggested these may indicate that after ADT	1) if/how the subsequent treatments in ARAMIS differ to the NHS 2) whether abiraterone and enzalutamide after darolutamide would be expected to have a treatment effect 3) whether survival on ADT alone in ARAMIS was shorter than would be expected in NHS practice because fewer people had follow on treatments with abiraterone or enzalutamide than in NHS clinical practice. **What additional information at engagement would help address the issue?** • Clinical expert clarification on likely treatment effect of abiraterone and enzalutamide if taken after darolutamide. • Additional data on survival on ADT alone (observational or trial), particularly for people who have had follow on treatments after ADT which reflect NHS practice.

Issue	Summary	Technical Team Preliminary Judgement
	alone, longer-term survival is greater with enzalutamide than abiraterone or docetaxel. However, the confidence intervals overlap, so the analysis is uncertain. • Analysing survival on follow on treatments in ARAMIS is difficult because: 1) there are small patient numbers 2) data are not randomised 3) data on subsequent treatments is not split by whether it was the first, second or third treatment after darolutamide + ADT or ADT alone and the treatment pathway in the trial may not reflect NHS. • ERG agree with company no easy way to deal with uncertainties in the trial overall survival data caused by differences in treatments used in the trial and expected UK clinical practice.	
Maturity of overall survival data *At the time of the final overall survival analysis most people in both arms are still alive* ***Why is this an issue?*** *Extent of survival benefit with darolutamide + ADT vs. ADT alone is uncertain because there is only survival data for a minority of the trial population*	• Trial results suggest that darolutamide + ADT increases overall survival compared with ADT alone; HR=[redacted] (event driven pre-planned final analysis November 2019). • ERG notes small number of events given the number of patients [redacted] • Company states that 240 overall survival events were planned for the analysis of overall survival; median survival time is not reached in either arm. • Company (factual accuracy check response to ERG report) note that not reaching median at the final data-cut in either arm is to be expected given the early stage of the disease and the reduced mortality risk with darolutamide - median is almost reached for ADT alone.	• The secondary endpoint of overall survival in ARAMIS met the criteria for being considered statistically significant outlined in the statistical analysis plan. • The maturity of the overall survival data from ARAMIS may affect the certainty around the overall survival estimates used in the cost effectiveness modelling. **What additional information at engagement would help address the issue?** • Clarification from the company/ clinical experts about whether any longer term follow up data are available for darolutamide + ADT or ADT alone.

Issue	Summary	Technical Team Preliminary Judgement
Clinical trial data used in the model *Company's partitioned survival model uses different data cuts for metastasis-free survival and for time on treatment and overall survival* ***Why is this an issue?*** *Using different datacuts may suggest more people stop darolutamide before metastasis than would happen in clinical practice, which may underestimate darolutamide treatment costs in the non-metastatic state*	• Company models 3 health states 1) non-metastatic hormone-relapsed prostate cancer 2) metastatic hormone-relapsed prostate cancer and 3) dead. • Time in the metastatic state is estimated by the difference between the overall survival and metastasis-free survival (MFS) curves. • Company uses September 2018 ARAMIS data cut for MFS and November 2019 data cut for overall survival and time on treatment in the non-metastatic state. • ERG expects time on treatment curve to be similar to MFS curve because few patients would stop treatment if disease is responding. However, 2019 time on treatment curve tracks further below the 2018 MFS curve than expected suggesting that a substantial proportion of people stop treatment before their prostate cancer metastasises. • ERG concerned company's approach greatly reduces darolutamide costs in non-metastatic state: could have large effect on cost-effectiveness. • Company does not present MFS data from November 2019 data cut so unclear if MFS and time on treatment curves are more similar at same datacut. • In absence of November 2019 MFS data, ERG attempted to align MFS more closely with time on treatment by using more pessimistic extrapolation of MFS (Gompertz in both arms) – used in ERG base case.	• Using different data cuts for metastasis-free survival and time on treatment is inappropriate. • Few people are likely to stop darolutamide before metastasis in clinical practice; the summary of product characteristics states that treatment should continue until metastatic progression. • In absence of data for metastasis-free survival from the November 2019 data cut, ERG scenario is relevant. **What additional information at engagement would help address the issue?** • Company to provide data from November 2019 data cut for metastasis-free survival if available.
Time on subsequent treatments after disease metastasis	• In the metastatic health state, costs and utility values are based on the time the company assumes people will spend on 3 lines of treatment followed by best supportive care.	• A partitioned survival model is an appropriate approach, but the limitations of this approach should be taken into account.

Issue	Summary	Technical Team Preliminary Judgement
Modelled time on subsequent treatments for metastatic disease are not based on ARAMIS trial data. The modelling of costs and quality of life on these treatments is inconsistent ***Why is this an issue?*** *Model does not capture:* • *Effect of modelled subsequent treatments on survival* • *How the choice of treatment for non-metastatic disease affects the duration (and cost) of subsequent treatments for metastatic disease*	• This in turn is based on data on median times on 1st, 2nd and 3rd treatments for metastatic disease from NICE technology appraisals of enzalutamide and abiraterone for people with asymptomatic or mildly symptomatic metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (TA377 and TA387 respectively). N.b for utility values the time spent on each follow-on treatment was based on the mean estimates from TA377. • The proportion of patients alive is based on extrapolated overall survival curve from ARAMIS - there is no link modelled between the modelled treatments for metastatic prostate cancer and survival in the metastatic health state. • ERG: proportionally more people in darolutamide arm have best supportive care as one the first 3 treatments for metastatic disease as well as for a prolonged period of time at 4th line. The length of time in 4th line state is longer in the darolutamide arm due to time in the metastatic state being dependent on the MFS and overall survival curves. These survival curves were extrapolated from ARAMIS trial data rather than the expected efficacy of subsequent treatments. • Other types of model such as a Markov models link time on subsequent treatments to overall survival. • ERG/company noted that the committee for TA580 (which used a semi Markov model) considered that splitting immature overall survival data by progression status introduced further uncertainty around the modelled survival projections, which outweighed benefits of more complex structure.	• The durations in the 1st, 2nd and 3rd progressed states should be consistent when calculating utility values and the proportions of people who transition to each subsequent line of therapy. **What additional information at engagement would help address the issue?** • Company to provide a scenario in which applied durations for 1st, 2nd and 3rd subsequent treatment states are consistent for the purpose of calculating utility values and proportions progressing to each subsequent line of therapy. It should ideally be recognised that durations on subsequent treatments do not always equate with time to progression.

Issue	Summary	Technical Team Preliminary Judgement
	• ERG: model structure adequately captures the nature of the disease, but there are limitations with respect to accurately capturing the expected costs and QALYs accruing in the metastatic health state: 1) costs are based on the median time people spend on each treatment in TA377 and TA387; ERG think it should be based on the mean values because the median could underestimate subsequent treatment costs for first treatment of progressed disease but overestimate progression through to subsequent lines of therapy 2) the assumptions about time on follow on treatments are different for the modelled costs and quality of life on these treatments.	
Monitoring costs *ERG suggests these are inconsistent with previous appraisals* ***Why is this an issue?*** *There is disagreement between the ERG and company on the most appropriate monitoring costs*	• Monitoring costs are based on small sample of NHS patients carried out by company. • ERG: costs appear low compared to previous appraisals. Particularly monitoring CT scans. • ERG clinical expert advised all patients would have outpatient appointment every 6 weeks and alternate between consultant-led and nurse-led appointments. The company included consultant-led appointments at approximately [redacted] in the non-metastatic state and [redacted] in the metastatic state. • ERG prefers estimates from TA580, enzalutamide for non-metastatic hormone-relapsed prostate cancer and uses this in its base case. • ERG also prefers Healthcare Resource Group costs (£194) for a consultant oncologist outpatient visit to the company's cost (£109) from Personal Social Services Resource Unit 2019 costs and uses the HRG costs in its base case.	• The frequency of disease monitoring appointments presented in the appraisal of enzalutamide for this indication (TA580) were considered reasonable by the appraisal committee. • Updated estimates of monitoring costs should be considered and clarification is needed on whether these represent current clinical practice. **What additional information at engagement would help address the issue?** • Clinical expert advice on monitoring frequency

Issue	Summary	Technical Team Preliminary Judgement
Plausibility of company modelled outcomes: Extrapolation of overall survival from trial *Company may overestimate proportion alive after 20 years on darolutamide* ***Why is this an issue?*** *Most of the overall survival data in the company model is extrapolated beyond the trial follow up. Choice of survival curve affects cost-effectiveness results.*	• Company extrapolated trial overall survival data separately for each arm using a Weibull distribution • ERG agreed statistical and observed fit to the trial data was reasonable • No long-term data to validate overall survival estimates. • ERG clinical expert considered implausible that people would survive to 20 years with hormone-relapsed prostate cancer (irrespective of having metastatic disease or not). Estimated proportion alive at 20 years would be somewhere between the company's preferred Weibull curve for darolutamide (2.3% alive at 20 years) and generalised gamma (0% alive at 20 years). • ERG used same distributions for extrapolating overall survival data in its base case as company - however, to address issue of time in metastatic health state (see next issue) ERG adjusted the darolutamide curve by equalising the mortality rate to extrapolated in the ADT arm from 5 years onwards. This forces a convergence with the ADT curve, and results in nobody surviving to 20 years in either modelled treatment arm.	• Long term survival estimates uncertain because they are extrapolated from trial data in which most people were alive. • Using the generalised gamma rather than the Weibull distribution to extrapolate overall survival in the darolutamide arm almost doubles cost-effectiveness estimate. • The appropriate method of extrapolating the data can be informed by assessing the plausibility of the long-term survival estimates. **What additional information at engagement would help address the issue?** • Additional data to validate long-term overall survival estimates. • Clinical expert opinion on 20-year survival rate. • Clinical expert opinion on expected survival following metastasis on ADT alone and on darolutamide, accounting for the different treatments available.
Plausibility of company modelled outcomes: time in metastatic health state *Company model suggests this is greater after darolutamide + ADT than after ADT alone. ERG consider this implausible* ***Why is this an issue?***	• Model outputs show that patients in darolutamide arm live longer in the metastatic health state than patients in ADT arm. • This is because the proportional reduction in the risk of dying with darolutamide compared with ADT is modelled to increase over time (even after people have stopped taking darolutamide or ADT). • ERG consider implausible because people having ADT for non-metastatic disease would have access to more treatments once cancer	• Appears implausible that there would be a survival benefit compared with ADT after stopping darolutamide. • Seems to be driven by patients in darolutamide + ADT arm gaining more life years when having BSC after 3 lines of treatment for metastatic disease than people in the ADT arm.

Issue	Summary	Technical Team Preliminary Judgement
There are no clinical data for how long people survive on the modelled treatments for metastatic disease after darolutamide + ADT vs after ADT alone and whether survival is different. The longer modelled survival after darolutamide + ADT may be a consequence of limitations in the modelling approach/clinical data informing the model.	metastasised so would be expected to live longer with metastatic disease than people who initially had darolutamide. • ERG agrees with company there is no easy way to adjust trial data so proposes exploring uncertainty by reducing the modelled survival benefit. • Scenarios (carried out by company) include: 1) Overall survival curves converge after 8.7 years. The choice of cut-off mirrors the data available in TA580 in which the effect of enzalutamide relative to ADT improves up to 8.7 years and tapers between 8.7 and 17 years (company submission) 2) hazard of mortality equalised between ADT arm and darolutamide arm from 5 or 7 years (company response to clarification questions). • ERG prefer equalising hazards of mortality after 5 years because its clinical expert believed the survival extrapolation for darolutamide to be overoptimistic and was more confident in the validity of the ADT extrapolation. It also has the effect of making the time spent with metastatic disease greater after ADT alone than after darolutamide + ADT.	• ERG scenario is relevant but the rationale for the 5-year cut off should be considered. **What additional information at engagement would help address the issue?** • Comments on plausibility of model outputs. • Comments on plausibility of scenarios.
Innovation/ benefits not captured in the model *Company and patient groups highlight an unmet need and the favourable safety profile of darolutamide. Patients stated that having no active treatment causes anxiety and*	• Company suggests darolutamide innovative because: 1) No NICE recommended first-line therapy for non-metastatic hormone-relapsed disease 2) Favourable safety profile compared with enzalutamide and apalutamide because does not cross blood-brain barrier. Less risk of seizures, falls, fatigue, mental impairment. Minimising such side effects important to patients.	• There may be an unmet need and an active treatment could be considered a step-change in treatment. • Although the safety profile of darolutamide is important, because enzalutamide and apalutamide are not used in NHS clinical practice the favourable safety benefits are not a step-change in current practice. • It is unclear how the anxiety of having no active treatment affects quality of life

Issue	Summary	Technical Team Preliminary Judgement
delaying time to symptomatic metastases important to them ***Why is this an issue?*** *The committee considers whether a technology is a step-change in treatment and whether there are benefits that have not been captured in the modelling in its decision making*	3) Can take other medications with darolutamide because has fewer drug–drug interactions • Patient groups state there is an unmet need and would welcome an active treatment at this position in treatment pathway. • Patient groups note anxiety of waiting for metastasis before they can have next treatment. This is especially the case for high-risk group who may see their monitored PSA levels are rising, but are aware that sometimes metastases may not be picked up by conventional monitoring methods. • Patient groups welcome that darolutamide may extend the time that people can live without symptoms and side effects. • The company assumed in its model that quality of life is the same when a person has darolutamide + ADT and when a person has ADT alone, based on data collected in ARAMIS.	when a person has non-metastatic prostate cancer. • It is also unclear whether quality of life data measured in a blinded trial (where people do not know if they are having darolutamide or not) would reflect the anxiety of people who are not participating in a trial. **What additional information at engagement would help address the issue?** • Clarification from clinical and patient experts on whether delaying time to metastasis from a median of 18 months to 40 months is a step-change in the management of non-metastatic hormone relapsed prostate cancer. • Clarification from patient experts on how living with the condition affects their quality of life.
• **No issues were identified with the utility values used in the model. N.b. the company updated its approach to modelling utility in the metastatic state in response to clarification**		

2 Questions for engagement

Treatment pathway

1. Is the company's assessment of the current treatment pathway and likely treatment pathway if darolutamide is available reasonable? (see table below) In particular, after having darolutamide for non-metastatic disease is it likely that:
    - no one is offered enzalutamide for metastatic disease
    - fewer people than currently are offered abiraterone for metastatic disease

- more people than currently are offered docetaxel for metastatic disease?

2. If this is the case, why would enzalutamide and abiraterone not be used after darolutamide?

Table shows company's proposed treatment pathway (based on figure 3 company submission document B)

	Company: current UK situation	**Company: if darolutamide available in clinical practice**
Treatment for non-metastatic hormone-relapsed disease	ADT	Darolutamide + ADT
1st treatment for metastatic hormone-relapsed disease **(% having each treatment)**	• Abiraterone + ADT (40-42.5%) • Enzalutamide + ADT (40-42.5%) • Docetaxel + ADT (10-15%) • No treatment / BSC (2-5%) • Radium-223 + ADT^ (0-3%)	• Abiraterone +ADT (1-5%) • Docetaxel + ADT (55-60%) • No treatment / BSC (15-20%) • Radium-223 + ADT^ (20%)
2nd treatment for metastatic hormone-relapsed disease	• 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%)	• Docetaxel + ADT (5-15%) • Radium-223 + ADT^ (20%) • No treatment / BSC (25-50%) • Abiraterone +ADT (1-10%) • Cabazitaxel + ADT (20-30%)
3rd treatment for metastatic hormone-relapsed disease	• No treatment / BSC (25-50%) • Cabazitaxel + ADT (20-30%) • Radium-223 + ADT^ (20%) • Docetaxel + ADT (5-15%) • Abiraterone +ADT (1-10%)	• No treatment / BSC (80%) • Cabazitaxel + ADT (10%) • Radium-223 + ADT^ (5-10%) • Abiraterone + ADT (0-5%)
^ after 2 lines of treatment or if not eligible for other treatments		

Generalisability of ARAMIS to UK practice

1. The table below shows the subsequent treatments in ARAMIS and those modelled by the company, which the company suggests reflects likely NHS practice (table 17 company response to clarification).
   - Are abiraterone or enzalutamide taken after darolutamide expected to be effective compared with docetaxel or with best supportive care? Would these treatments be offered after darolutamide in NHS clinical practice?
   - Are overall survival estimates from ARAMIS likely to underestimate survival for ADT alone because fewer people had abiraterone or enzalutamide after ADT alone than is seen in NHS clinical practice?

Subsequent treatment	Treatments after progression: September 2018 data cut		Treatments after progression: November 2019 data cut		First treatment for metastatic disease in NHS (used in model)	
	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%

Maturity of overall survival data

1. Are there any long-term data for survival in people who had darolutamide + ADT or ADT alone for non-metastatic hormone-relapsed prostate cancer?

Company model: clinical trial data used in the model

1. Would most people continue darolutamide until their cancer metastasised?
2. In absence of metastasis-free survival data from the November 2019 data cut, is the ERG approach of using a Gompertz curve to align metastasis-free survival with time on darolutamide treatment appropriate?
3. Company please provide metastasis free survival from the November 2019 data cut if available.

Company model: approach of modelling time on subsequent treatments after disease metastasis

1. Company to provide a scenario in which consistent durations on 1st, 2nd and 3rd treatments for metastatic prostate cancer are used when applying weighted costs and utility values in the model

Monitoring costs

1. Which monitoring assumptions better reflect NHS clinical practice, the company's or the ERG's?
2. What is the cost of a consultant-led outpatient appointment: £194 (ERG estimate) or £109 company estimate?

	Non-metastatic hormone-relapsed		**Metastatic hormone-relapsed**	
	Company base case: (IQVIA study)	**ERG base case: TA580**	**Company base case: (IQVIA study)**	**ERG base case: TA580**
Outpatient visit - Consultant	[redacted]	Every 12 weeks	[redacted]	Every 12 weeks
Outpatient visit - nurse	[redacted]	Every 12 weeks	[redacted]	Every 12 weeks
Community nurse visit	[redacted]	Every 6 weeks	[redacted]	Every 6 weeks
CT scan	[redacted]	Every 12 weeks	[redacted]	Every 12 weeks

Plausibility of company modelled outcomes: extrapolation of overall survival estimates from trial data

1. Are there any data to validate the company's long-term overall survival extrapolations?
2. Would you expect any people to be alive 20 years after diagnosis with non-metastatic hormone-relapsed prostate cancer?

Plausibility of company modelled outcomes: time in metastatic health state

1. Is it plausible that the survival benefit in the metastatic health state would be longer after darolutamide + ADT than ADT alone? Is there a treatment benefit after stopping darolutamide?
2. Given that there may be more treatment options available after ADT alone, would it be expected that survival with metastatic prostate cancer is longer after ADT alone after than after darolutamide + ADT?
3. Are the ERG's scenarios appropriate for addressing uncertainty? Would there be no relative survival benefit with darolutamide + ADT over ADT alone after 5 years?

Innovation/ benefits not captured in model

1. Is the clinical effect seen in ARAMIS (delaying median survival without metastases from 18 to 40 months) a step-change in the management of non-metastatic hormone-relapsed prostate cancer?
2. How does the anxiety of anticipating progression to metastatic disease affect quality of life? Would being in a clinical trial in which you could be having a new treatment relieve this anxiety? How would knowing that darolutamide may delay this disease progression affect quality of life?