NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Darolutamide with androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer [ID6452]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

COST COMPARISON APPRAISAL

Darolutamide with androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer [ID6452]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission** from Bayer:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submission** from:
   a. Prostate Cancer Research
   b. Prostate Cancer UK
   c. Tackle Prostate Cancer
   d. British Uro-Oncology Group
   e. Royal College of Pathologists

4. **NICE medicines optimisation team (MOT) report**

5. **External Assessment Report** prepared by Southampton Health Technology Assessments Centre (SHTAC)

6. **External Assessment Group response to factual accuracy check of EAR**

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: cost-comparison

Darolutamide with androgen deprivation therapy for treating metastatic hormone-sensitive prostate cancer [ID6452]

Document B

Company evidence submission

April 2025

File name	Version	Contains confidential information	Date
ID6452_darolutamide ADT mHSPC_Doc B_[Redacted]	V.1	Yes	17/04/25

Contents

Tables and figures

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

B.1.1 Decision problem

The submission covers the full population for the comparator, as recommended by NICE. Accordingly, darolutamide is submitted for reimbursement in combination with androgen deprivation therapy (ADT) as an option for treating adult men with hormone-sensitive metastatic prostate cancer (mHSPC) who are unsuitable for docetaxel.

This positioning is fully aligned with the population for which apalutamide has received a positive recommendation from NICE (TA741, published 28 October 2021):

- Apalutamide plus ADT is recommended as an option for treating mHSPC in adults, only if: docetaxel is not suitable.

Apalutamide + ADT is the most appropriate comparator for this assessment. In addition to their shared mechanism of action and identical positioning in the treatment pathway, supported by validation through a clinician advisory board, results from a clinician-validated indirect treatment comparison (see Section B.3.9) suggest darolutamide and apalutamide demonstrate similar efficacy in the treatment of mHSPC. This supports the conclusion that a cost-comparison approach is the most suitable and appropriate methodology for this appraisal.

The decision problem addressed within this submission is outlined in Table 1.

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	People with hormone-sensitive metastatic prostate cancer	Adult men with mHSPC who are unsuitable for chemotherapy.	As per scope
Intervention	Darolutamide with androgen deprivation therapy	Darolutamide with androgen deprivation therapy	As per scope
Comparator(s)	For people in whom docetaxel is not suitable: • Apalutamide and androgen deprivation therapy • Enzalutamide and androgen deprivation therapy	Apalutamide with androgen deprivation therapy	As this submission is a cost comparison, we have compared darolutamide with a single NICE-recommended comparator, apalutamide. NICE technology appraisal 741 recommends apalutamide at the same point in the treatment pathway with the same wording as is anticipated for darolutamide. That is, apalutamide is recommended for people with mHSPC who are unsuitable for chemotherapy.
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rate • Time to hormone relapsed prostate cancer	The outcome measures to be considered include: • Overall survival • Radiographic progression free survival • Time to castration resistant prostate cancer • Time to subsequent therapy	**Radiographic progression free survival (rPFS)** was the primary endpoint in the ARANOTE study. **Response rate** was not a pre-planned endpoint in the ARANOTE study and thus these data will not be included in this submission. Response rate is not generally used

	• Time to subsequent treatment • Prostate-specific antigen undetectable rate • Time to prostate-specific antigen progression • Time to pain progression • Adverse effects of treatment • Health-related quality of life.	• Prostate-specific antigen undetectable rate • Time to prostate-specific antigen progression • Time to pain progression • Adverse effects of treatment • Health-related quality of life.	as an outcome measure in advanced prostate cancer, as prostate metastases, particularly bone metastases, generally do not show radiological responses to treatment, even though overall the treatment may be working.
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. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any	Cost-comparison model considered from an NHS perspective	

	differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.		
Subgroups to be considered	If the evidence allows, the following subgroups of people will be considered: • people with newly diagnosed metastatic prostate cancer • people with high-risk metastatic prostate cancer	No subgroups	**Adult men with newly diagnosed metastatic prostate cancer** Both patients with M1 (*de novo*) and M0 (recurrent) at initial diagnosis have been included in ARANOTE. The majority of patients (72.5%) were *de novo* and the results in ARANOTE have been consistent across these subgroups. Therefore, the appraisal has focused on the ITT population. Consistency between these subgroups gives further re-assurance that darolutamide is similarly efficacious in both newly

			diagnosed *de novo* patients and patients with mHSPC in general. **Adult men with high-risk metastatic prostate cancer** It is not clear what the high-risk metastatic prostate cancer definition is in the scope. ARANOTE has been stratified by extent of disease (i.e. non-regional lymph node metastasis, bone metastasis, and visceral metastasis). The efficacy observed in ARANOTE was consistent across these three subgroups. There was no classification by 'high-risk' disease in ARANOTE. There is inconsistent use of 'newly diagnosed' and 'high risk' for randomisation across all mHSPC trials. Furthermore, although appraisals for apalutamide in mHSPC also listed these subgroups in their scopes they were never explored by the submitting company nor was the lack of data in these subgroups highlighted as a key issue during

			the appraisal. As such, this appraisal has focused on the ITT population.
Special considerations including issues related to equity or equality	[please delete row if not applicable]	Current systemic treatment options for mHSPC, such as apalutamide and enzalutamide, are not recommended for patients with a history of seizures, and these patients were excluded from the pivotal trials (TITAN[1] and ARCHES,[2] respectively). In clinical practice these patients would have to be treated with docetaxel + ADT or ADT monotherapy alone. This exclusion highlights a small but significant gap in the treatment pathway, leaving an underrepresented group of patients without effective treatment options. In contrast, the ARANOTE trial allowed patients with a medical history of seizures to participate.[3, 4] This underscores an important unmet need for effective and safe treatment options for this specific but meaningful group of patients. In ARANOTE, one patient with a history of seizure was included, and there were no reports of seizure in ARANOTE.[3, 4] In ARASENS, six patients with a history of seizure	

		were included, none of the four patients in the darolutamide arm with a history of seizure experienced a TEAE of seizure.[5] In addition, in ARAMIS, the pivotal trial for darolutamide in the nmCRPC setting, the incidence of seizure was low (0.2%) and consistent between the darolutamide and placebo arms.[6] Patients with mHSPC often have multiple comorbidities (e.g. hypertension and atrial fibrillation) requiring polypharmacy,[7-10] leading to a significant risk of drug-drug interactions with apalutamide, which has potential of 310 known DDIs, as reported by the BNF.[11] Darolutamide is known to have fewer than 45 potential interactions[12] and suggests use of darolutamide will mean easier monitoring and patient management.[12] Furthermore, apalutamide has a moderate level interaction with relugolix, a newer oral ADT and is to be avoided or dose adjusted in combination.[13, 14]	

B.1.2 Description of the technology being evaluated

Darolutamide is a structurally distinct non-steroidal androgen receptor (AR) inhibitor for the treatment of patients with prostate cancer.[15] Both darolutamide and its active metabolite inhibit testosterone-induced translocation of ARs to the nucleus, decreasing the activation of genes required for the growth and survival of prostate cancer cells.[15, 16]

Although darolutamide fundamentally has the same mechanism of action to the other second generation anti-androgens, such as apalutamide, it is a more polar molecule, with a flexible structure, and hydrogen bond-forming potential.[15, 17-19] These structural features mean darolutamide displays low blood-brain barrier (BBB) penetration compared with other AR targeted agents (ARTAs), such as apalutamide, in pre-clinical models.[20, 21] Darolutamide's limited penetration of the blood brain barrier may be associated with fewer central nervous system (CNS) adverse events (e.g., fatigue, seizures, and cognitive/mental impairment disorders).[20-22]

Darolutamide also has fewer drug-drug interactions (DDI) than apalutamide in patients with prostate cancer, reinforcing its strong safety profile and making it a highly favourable choice, particularly for patients who require complex medication regimens.[11, 12, 23] This advantage enhances treatment tolerability and minimises the risk of complications associated with polypharmacy, ultimately contributing to improved patient outcomes.[24]

A summary description of darolutamide is presented in Table 2. The draft summary of product characteristics (SmPC) is provided in Appendix C.

Table 2. Technology being evaluated

UK approved name and brand name	UK approved name: Darolutamide Brand name: (Nubeqa®)
Mechanism of action	Darolutamide is an 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.[15, 25] These structural features mean darolutamide displays low BBB penetration compared with apalutamide and enzalutamide in pre-clinical models.[20, 21] Darolutamide's limited penetration of the BBB and low binding affinity for

	γ-aminobutyric acid type A (GABA-A) receptors may be associated with fewer CNS adverse events than other second generation anti-androgens.[15, 20-22] A major metabolite, keto-darolutamide, exhibits similar *in vitro* activity to darolutamide. Darolutamide treatment decreases prostate tumour cell proliferation leading to potent antitumour activity.
Marketing authorisation/CE mark status	Darolutamide with androgen deprivation therapy (ADT) is currently awaiting marketing authorisation in the UK for treating metastatic hormone-sensitive prostate cancer (mHSPC). Darolutamide was filed with the MHRA for this licence extension on [redacted] with approval expected in [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated indication for darolutamide is for 'the treatment of adult men with metastatic hormone sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy'.
Method of administration and dosage	The recommended dose of darolutamide is 600 mg (two 300 mg film-coated tablets), twice daily, equivalent to a total daily dose of 1200 mg. Darolutamide is for oral use. Tablets should be swallowed whole and taken with food. No dose adjustment is required in mild or moderate renal impairment or mild hepatic impairment. For patients with severe renal impairment (eGFR 15-29 mL/min/1.73 m^2) not receiving haemodialysis, the recommended starting dose is 300 mg twice daily. For patients with moderate and severe hepatic impairment (Child-Pugh Classes B and C), the recommended starting dose is 300 mg twice daily. Medical castration with a luteinising hormone-releasing hormone (LHRH) agonist or antagonist (GnRH analogue) should be continued during treatment of patients not surgically castrated. If a patient experiences a ≥Grade 3 toxicity or an intolerable adverse reaction related to darolutamide, dosing should be withheld or reduced to 300 mg twice daily until symptoms improve. Treatment may then be resumed at a dose of 600 mg twice daily.
Additional tests or investigations	No additional tests or investigations are required.
List price and average cost of a course of treatment	List price: £4,040.00 (112 x 300mg tablets), for 28 days of treatment.
Patient access scheme/commercial arrangement (if applicable)	Darolutamide is available to the NHS with a confidential discount of [redacted]% on the price per pack

Abbreviations: ADT: androgen deprivation therapy; BBB: blood brain barrier; CNS: central nervous system; GABAA: γ-aminobutyric acid type A; eGFR: glomerular filtration rate; GnRH: gonadotropin releasing hormone; LHRH: luteinising hormone-releasing hormone; MHRA: Medicines and Healthcare products Regulatory Agency; mHSPC: metastatic hormone-sensitive prostate cancer; OS: overall survival; rPFS: radiological progression-free survival.

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

Summary

- Prostate cancer is the most common cancer diagnosis in England.[26] A total of 1 in 8 men will be diagnosed with prostate cancer in the UK, and over 10,000 men will die from it each year in England.[27]
- Metastatic prostate cancer can be defined as metastatic hormone sensitive prostate cancer (mHSPC) and metastatic castration resistant prostate cancer (mCRPC).[28-31]
- Patients with mHSPC ultimately progress to mCRPC, the final disease stage, associated with increased morbidity, HRQoL deterioration, increased economic burden and poor survival;[28, 29, 32-36] delaying mHSPC progression to mCRPC is a key goal of treatment.[37, 38]
- mHSPC disease-related symptoms are very common, resulting in significant clinical burden.[39-44] Fatigue is common, found in 66–77% of patients[45] and reported by patients with prostate cancer to be one of its most burdensome symptoms.[46-52]
- The highest prevalence of prostate cancer in the UK occurs in older men, who are more likely to experience considerable comorbidities and require polypharmacy.[7] This results in an increased risk of DDI's, adding a notable level of complexity to treatment decisions.[8, 9, 53]

Prostate cancer is the most common cancer diagnosis in England,[26] with the National Prostate Cancer Audit reporting a total of 55,241 and 2,521 men were diagnosed with prostate cancer in England in 2023 and Wales in 2022. A total of 1 in 8 men will be diagnosed with prostate cancer in the UK, and over 10,000 men will die from prostate cancer each year in England.[27]

Risk factors for prostate cancer include older age (prostate cancer is most frequently diagnosed in males aged 65 to 74 years[54]), prostate-specific antigen (PSA) level, obesity, a family history of prostate cancer, and ethnicity.[55] The risk of developing

prostate cancer is significantly higher in Black African males than in White or Asian males.[56] In the UK, 1 in 4 Black men will get prostate cancer in their lifetime, and 1 in 12 Black men will die from prostate cancer.[27]

Pathophysiology and disease targets

The development, growth, and survival of prostate cells, both normal and cancerous, depends on androgens (e.g., testosterone) and the AR pathway.[57] Androgen stimulation is a major driver of progression in prostate cancer, with the overexpression and hypersensitivity of ARs being important factors in both the development of metastases and castration resistance.[57] The AR pathway is therefore a key target for agents used in the treatment of prostate cancer.

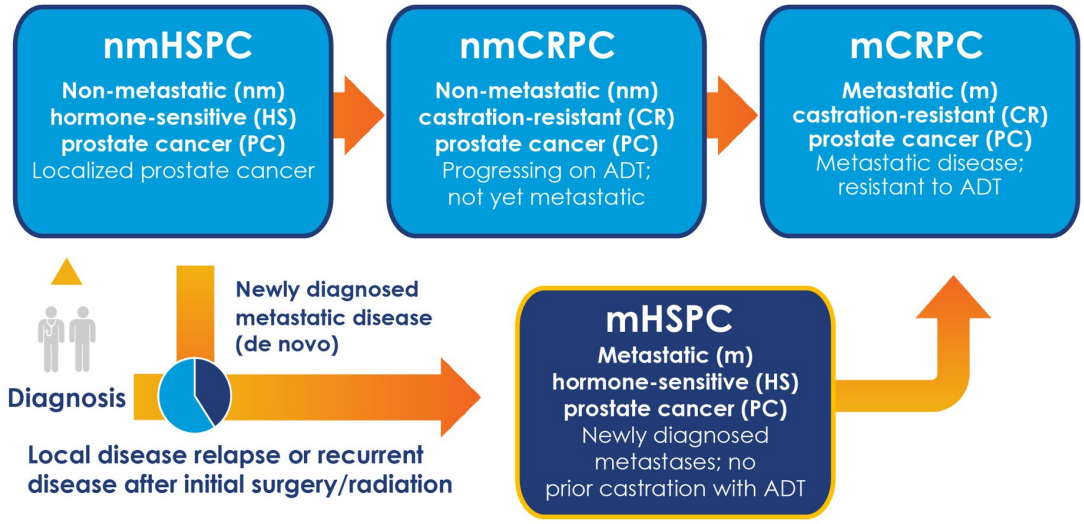
Androgen deprivation therapy (ADT) via surgical or medical castration, which centrally targets the AR signalling pathway, was used historically to achieve castrate levels of testosterone.[37] However, a more effective recommended treatment approach is combining ADT with an AR targeted agent (ARTA), such as an androgen synthesis inhibitor (ASI) or second-generation AR inhibitor (SGARI).[38] This combination works synergistically, optimising blockade of the AR pathway through complementary mechanisms, and enhancing the anti-tumoural treatment-effect.[37]

Diagnosis and disease state

The diagnostic pathway for prostate cancer aims for the timely detection of significant prostate cancer.[58] Men with a PSA >1ng/ml at 40 years or >2ng/ml at 60 years are at increased risk of prostate cancer metastasis or death from prostate cancer.[55] In men with elevated PSA, a prostate cancer risk calculator (based on age, ethnicity, family history, PSA level, free/total PSA ratio, and findings on digital rectal examination) and/or multiparametric magnetic resonance imaging (mpMRI) determines the need for prostate biopsy.[55] Results from these diagnostic tests determine whether the disease is localised or advanced/metastatic. Based on 2018 data from Cancer Research UK (as the most recent year that followed typical trends), 48.6% of men have localised prostate cancer (Stage I and II, based on TMN classification [59]) at the time of diagnosis, 40.4% have metastatic disease (Stage III and IV), and 11.0% have unknown staging.[60]

Figure 1 describes the distinct clinical disease states at diagnosis and the different stages of progression of prostate cancer.[28, 29] A survey of 120 physicians conducted in 2023 in EU5 (France, Germany, Italy, Spain, and UK) reported 31% of men living with prostate cancer had non-metastatic hormone-sensitive PC (nmHSPC), 15% had non-metastatic castration-resistant prostate cancer (nmCRPC), 25% had metastatic hormone-sensitive prostate cancer (mHSPC), and 29% had metastatic castration-resistant prostate cancer (mCPRC).[59]

Figure 1. Clinical states of PC



Abbreviations: ADT: androgen deprivation therapy; mCRPC: metastatic castration-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; nmCRPC: nonmetastatic castration-resistant prostate cancer; nmHSPC: nonmetastatic hormone-sensitive prostate cancer; PC: prostate cancer.

Sources: Adapted from Scher 2016[28] and Scher 2015.[29]

The mHSPC population includes patients with metastases detectable using conventional imaging who are newly diagnosed (*de novo* mHSPC) and have not received ADT, or have recurrent mHSPC and either have not received or are continuing to respond to ADT.[29-31] mHSPC pivotal clinical trial cohorts typically included both *de novo* and recurrent patients. The abiraterone + docetaxel PEACE study cohort, which included only newly diagnosed mHSPC, is a notable exception.[55, 61, 62]

De novo mHSPC typically has a more aggressive clinical course than recurrent mHSPC, and is associated with worse survival of 6.2 years versus 11.6 years in patients with primary progressive disease.[63] Other factors associated with poor prognosis include high-volume disease, a Gleason score ≥8, the presence of

measurable visceral metastases, and ≥3 bone metastases.[64] Disease-related factors such as skeletal-related events (SREs) and pain (both commonly caused by bone metastases) also negatively affect survival outcomes in mHSPC.[46, 65-67]

Patients with mHSPC will ultimately progress to mCRPC, the final clinical state of prostate cancer. mCRPC is linked to increased clinical morbidity, deterioration in HRQoL, increased economic burden, and poor survival.[28, 29, 32-36] As such, the most important treatment goal in mHSPC is delaying disease progression to mCRPC.[37, 38]

Burden of mHSPC

mHSPC disease-related symptoms are very common which results in a significant clinical burden.[39-44] Patients frequently experience symptoms such as fatigue (73%), urinary symptoms (63%), sexual dysfunction (62%), and bone pain (52%).[68] Other symptoms common to mPC include difficulty sleeping, weakness/numbness in extremities, and weight loss.[68]

Patients and clinicians report fatigue as one of prostate cancer's most burdensome symptoms and it is highly correlated with poor HRQoL.[46-49] Fatigue makes it difficult for men to conduct activities of daily living, such as personal care, social activities, and work,[49] leading to decreased productivity, emotional strain and a greater need for supportive care.[50-52] As well as being related to the disease itself, treatment for prostate cancer can also cause fatigue.[49] Patients treated with ADT commonly experience fatigue,[58] while fatigue was one of the most frequently occurring adverse events (AEs; All Grades) in the TITAN and ARCHES pivotal phase III studies in mHSPC for the second generation ARTAs apalutamide and enzalutamide.[2, 49, 69] Treatment-related toxicities are discussed in further detail in Section B.1.3.2.

Patients with mHSPC experience significant HRQoL burden due to mHSPC-related symptoms and treatment-related toxicities that negatively affect daily functioning.[50-52] Furthermore, fear of progression is found in ~15% of patients with mHSPC, and is linked to mental health symptoms, such as depression and anxiety.[70] HRQoL deteriorates substantially with progression from mHSPC to mCRPC, thus delaying progression is essential to maintaining patient quality of life.[36, 71]

Prostate cancer has a higher prevalence in males of older age who are more likely to have significant comorbid conditions requiring polypharmacy in addition to the anti-cancer treatment.[7-9] A US-based study reported patients with prostate cancer take a median of 10 concomitant medications (IQR: 7–14; N=1,430; SEER database and Medicare claims data; 1991–2013).[10] The risk of DDIs with mHSPC medications is a key concern with current treatments for mHSPC and adds a significant level of complexity to treatment decisions.[53] The National Prostate Cancer Audit, reported that only 13.9% of patients with two or more morbidities (as per the Charlson Comorbidity Index) received optimum mHSPC therapy with treatment intensification.[72] The British National Formulary (BNF) reports as many as 310 and 233 potential interactions for apalutamide and enzalutamide, respectively.[11, 23] These include interactions with medications used to treat common long-term conditions in patients with mHSPC, such as cardiovascular disease, atrial fibrillation and hypertension. The impact of potential DDIs on patients and their management is discussed in more detail in Section B.1.3.2.

Epidemiology

The National Prostate Cancer Audit reported total of 55,241 and 2,521 men were diagnosed with prostate cancer in England in 2023 and Wales in 2022, respectively, a year-on-year increase of 9% in England and 26% in Wales.[73] Epidemiology data on mHSPC are limited, but estimates suggest the rate of mHSPC is rising, including in patients of a younger age (45–75 years).[74, 75] A total of 13% of new prostate cancer cases between 2018 and 2020 in England were classed as *de novo* mHSPC, with an estimated total 7,213 cases of *de novo* mHSPC in the UK.[76, 77]

The overall median five-year survival rate is 86.6% for patients with prostate cancer, but, when diagnosed at a metastatic stage, the five-year survival rate drops to 49%.[54, 78] Reduced survival is predominantly due to the progression of mHSPC to mCRPC,[79] highlighting the significant need to optimise mHSPC treatment and delay disease progression to mCRPC.[37, 38]

B.1.3.1 Clinical pathway of care

Summary

Clinical pathway of care

- NICE, ESMO and EAU guidelines for mHSPC treatment are currently followed in England;[58, 61, 80, 81] though there has been significant change in the treatment landscape since NICE guidance was last updated.[81]
- ESMO guidance for mHSPC recommends ADT monotherapy only in vulnerable men unable to tolerate treatment intensification[61]; in England and Wales, 5–20% receive ADT monotherapy,[72, 80, 82] with a UK Delphi panel confirming ADT monotherapy should not be offered to new patients unless they decline or are unfit for treatment intensification.[83]
- Current ESMO guidance recommends darolutamide + ADT + docetaxel or an ARTA + ADT as first-line therapy for mHSPC[61]; ADT + docetaxel is not recommended if an ARTA is available and its use is not contraindicated.[58]
- Patients with mHSPC unsuitable for cytotoxic docetaxel, receive ARTA (apalutamide or enzalutamide) + ADT doublet therapy (currently 70–80% patients in England and Wales).[61]

Product positioning and patient access

- Darolutamide + ADT is positioned for the treatment of mHSPC in patients who are ineligible for chemotherapy, with apalutamide as the key comparator based on its identical positioning in the treatment pathway, and it being from the same drug class with the same mode of action and administration, an approach validated by UK clinicians.[80]
- The docetaxel-ineligible patient population is a NICE and NHS England-defined population in prostate cancer,[84 85, 86] where patients are identified on a case-by-case basis through a clinician assessment within a defined clinical framework of individual patient risk.[84, 86]
- Consultant specialists in England and Wales access apalutamide for their patients through the National Cancer Drugs Fund by completing a Blueteq form with defined access criteria.[87]

During an expert advisory board meeting conducted in December 2024, clinicians advised that NICE, ESMO and EAU guidelines are currently followed in England for the treatment of mHSPC.[58, 61, 80, 81] For several decades, ADT monotherapy, via surgery (orchiectomy) or medical castration (e.g. using luteinizing hormone releasing hormone [LHRH] agonists/antagonists) was the standard of care for mHSPC.[37] However, this treatment strategy has been surpassed by more effective treatment intensification regimens.[88] ESMO 2023 treatment guidelines advise ADT monotherapy should only be used in vulnerable men who are unable to tolerate treatment intensification.[61] Expert clinicians confirmed that use of ADT monotherapy in England and Wales is restricted to use in patients with limited life expectancy, such as those who are very elderly, have widespread disease, and/or with multiple comorbidities.[80, 82] Only a small percentage of patients in England and Wales still receive ADT monotherapy (5–20%), with variations in practise among multidisciplinary teams and different healthcare institutions.[72, 80, 82] Results from a modified Delphi panel study of responses from 120 healthcare professionals in the UK (70 based in England) agreed ADT monotherapy should not be offered to new patients unless they decline or are unfit for treatment intensification.[83] A recent study suggests significant under-use in England of treatment intensification. Among 29,713 patients, use of treatment intensification between 2018–2022 was 39.0%.[72] The practice of treatment intensification decreases with age, frailty, comorbidities, socioeconomic deprivation, as well as among Black patients. Only 16.8% (n=2,404) of men aged ≥75 years had a record of treatment intensification vs 59.8% (n=9,184) of those aged <75 years.[72]

Current NICE guidelines for treatment of newly diagnosed mHSPC (NICE Clinical Guideline 131), recommend patients begin docetaxel chemotherapy within 12 weeks of ADT.[81] Although NICE guidelines are still in date, they were first published in May 2019 and last updated in December 2021.[81] The treatment landscape has significantly changed since then, as newer treatment options have become available. Recently updated EAU 2025 guidelines state that docetaxel as a sole addition to ADT is no longer a valid treatment option if an ARTA is available and its use is not contraindicated, in addition these updated guidelines now also recommend darolutamide + ADT in the mHSPC setting.[58] At a medical expert advisory board,

clinicians were unanimous that docetaxel + ADT is no longer a standard of care in England.[80]

Current ESMO guidelines followed by clinicians in England and Wales recommend triplet therapy with darolutamide + ADT + docetaxel or an ARTA + ADT as first-line therapy for mHSPC.[61] Darolutamide based triplet therapy was recommended based on its significant OS survival benefits over ADT + docetaxel observed in the phase III ARASENS study.[61] In ARASENS, risk of death from mHSPC was significantly reduced by 32.5% (HR, 0.68; 95% CI 0.57–0.80; p<0.001).[89] At a medical expert advisory board, clinicians practicing in England and Wales confirmed if patients are fit for chemotherapy, they would be nominated for first-line triplet therapy with darolutamide + ADT + docetaxel.[80] Currently between 10–20% of patients England and Wales receive triplet therapy. However, docetaxel is a cytotoxic agent and not suitable for use in all patients.[90, 91] Clinicians confirmed a majority of patients in England and Wales with mHSPC receive an ARTA (apalutamide or enzalutamide) + ADT doublet therapy (70–80%).[80] Clinical trials show combining ADT with an ARTA improves radiographic progression free survival (rPFS) and overall survival (OS) in mHSPC. In the TITAN pivotal trial, ADT plus apalutamide vs placebo reduced the risk of rPFS or death (HR, 0.48; P<0.001), as well as increasing overall survival at 24 months (82.4% vs. 73.5% for apalutamide vs placebo; HR, 0.67; P=0.005).[1]

Darolutamide + ADT is positioned as a treatment option for mHSPC in patients who are ineligible for docetaxel, in alignment with treatment guidelines followed in England and Wales, and validated by clinician opinion.[80] The key comparator to darolutamide in this cost-comparison submission is apalutamide, an existing NICE-recommended treatment option in an identical position in the treatment pathway, as well as being from the same drug class, and having the same mode of action and administration. This approach has been validated by UK clinicians.[80, 82]

Docetaxel ineligibility

The docetaxel-ineligible patient population is a clinically defined population, as set out in NICE technology appraisal TA741 for apalutamide plus ADT (in mHSPC),[84] NICE technology appraisal TA412 for Radium-223 dichloride (in mCRPC),[85] and in an NHS England Clinical Commissioning Policy Statement (in mHSPC).[86] Briefly, a clinical

framework of individual patient risk is used to define chemo-ineligibility, based on clinician assessment of risk-benefit profile on a case-by-case basis.[84] Contraindications for docetaxel may include those with:

1. Severe prior hypersensitivity reaction to taxanes.
2. Poor overall performance status (WHO performance status 3-4, caution for those with performance status 2).
3. Pre-existing significant peripheral neuropathy.
4. Poor bone marrow function due to extensive disease or other prior haematological problems.
5. Significant co-morbidity (e.g. cardio-vascular or respiratory disease) such that prostate cancer is not likely to be the life limiting illness for the patient.[84, 86]

Some patients diagnosed with mHSPC may have no or few symptoms, and believe docetaxel treatment may worsen their quality of life.[84] Thus, patients who choose not to have docetaxel are also considered docetaxel ineligible.[84]

In order for consultant specialists in England and Wales to access apalutamide for their patients, they must complete a Blueteq form. Details of the access criteria set out by the National Cancer Drugs Fund may be found in Appendix K.[87]

At a recent advisory board, clinicians in England and Wales stated that they do not currently use any formal assessment tools to determine if their patients are fit for chemotherapy but rely upon their clinical acumen, evaluating patients on an individual basis based on their fitness, comorbidities, their medication list and medical history. Clinicians also note that patients choice is a determinant.[80] Findings from a Delphi panel agreed that treatment selection should be tailored to the individual, based on a risk-benefit assessment, and that patient factors, such as fitness, comorbidities and preference, should be considered.[83]

B.1.3.2 Unmet need

Summary

- Additional treatment options are required for the heterogeneous mHSPC patient population, particularly those of older age,[1] those who are frail, and/or those with comorbidities who require polypharmacy.[92-97]
- Suboptimal treatment is associated with worse patient outcomes in mHSPC[98] and approximately 5–20%[72, 80, 82] of UK patients with mHSPC still receive suboptimal ADT monotherapy, due to concerns of tolerability and DDIs with treatment intensification.[9, 99-101]
    - Docetaxel is cytotoxic, meaning triplet therapy is unsuitable for many patients, and whilst a majority of patients with mHSPC receive an ARTA + ADT (70–80%),[80] both apalutamide and enzalutamide are associated with significant treatment-related toxicities and DDIs.[1, 2, 45, 102, 103]
- Treatment-related toxicities with current therapies (especially fatigue and rash prevalent with apalutamide use) lead to significant patient and healthcare resource use (HCRU) burden, affecting patient care and outcomes, requiring increased visits to healthcare providers (HCPs), polypharmacy to manage adverse events, and potential dose interruptions or mHSPC drug discontinuation.
- Patients treated with apalutamide show a significant increase in hypothyroidism[1] and clinicians in England and Wales confirm that thyroid testing required with apalutamide use leads to an increase in HCRU.[82]
- ARASENS,[44, 89] ARAMIS[16] and ARANOTE[3] trials demonstrate darolutamide has a favourable tolerability profile, with low incidences of ARTA-relevant AEs that impact patient activities of daily living (ADL).[3] ARAMIS and ARANOTE are the only phase III trials in mHSPC to show a placebo-like tolerability profile.[3, 16]

[1] PC is most frequently diagnosed in males aged 65 to 74 years.

- The risk of DDIs is a key concern in patients with mHSPC as they are generally elderly with multiple comorbidities requiring polypharmacy.[24, 104-108] DDI risk impacts both patients and HCPs, and results in substantial HCRU from the need for multidisciplinary team engagement to identify potential DDIs and select suitable treatment alternatives prior to initiation of treatment for the mHSPC[80]
- The BNF reports apalutamide and enzalutamide interact with a high number of medications (310 and 233 respectively),[11, 23] including those used for treating common comorbidities in mHSPC, such as cardiovascular disease (CVD); fewer than 45 potential DDIs are reported for darolutamide.[12] The safety of darolutamide was confirmed in the ARAMIS study where 98.4% of patients were receiving polypharmacy.[109]
- Preventing progression to mCRPC is a key treatment goal of mHSPC therapy; however more patients on apalutamide[1, 110] and enzalutamide[2] than placebo discontinue treatment.[3] ARANOTE is the only study in mHSPC to show lower discontinuation rates due to AEs in the treatment arm vs placebo, meaning patients stay on beneficial treatment for longer.[3]
- APCCC 2024 consensus opinion views darolutamide as a better tolerated treatment option than apalutamide or enzalutamide in patients with advanced cancer, with pre-existing comorbidities, and for older patients.[111]
- Clinicians in England and Wales confirm darolutamide's differentiated tolerability and low potential for DDI's, may simplify treatment management and allow treatment intensification in patients with comorbidities and risks of DDIs that make them ineligible for currently available treatments.[80]

Although treatment intensification regimens show clear survival benefits,[1, 2, 69, 89, 112] a recent report on treatment patterns of patients with mHSPC in England suggests significant underuse of treatment intensification, particularly among older, frail and socioeconomically deprived patients, as well as those with comorbidities.[72] Additional treatment options are needed to serve the heterogeneous mHSPC patient population, particularly for the aforementioned patient demographic.[92-97] Suboptimal treatment is

associated with worse patient outcomes in mHSPC[98] and a significant number of patients in the UK (5–20%, varying among treatment centres[80]) still receive suboptimal ADT monotherapy, due to concerns of tolerability and DDIs with treatment intensification regimens.[9, 82, 99-101] While treatment guidelines recommend use of darolutamide + ADT + docetaxel triplet therapy, docetaxel is known to increase risk of Grade 3–5 AEs, neutropenia, and neuropathy, thus a significant number of patients are ineligible for chemotherapy or choose not to receive it.[90, 91, 113, 114] The majority of patients in England are therefore treated with an ARTA + ADT doublet (70–80%).[80]

Whilst ARTA-doublet therapies are effective in slowing progression to mCRPC, both apalutamide and enzalutamide are associated with a range of concerning treatment-related toxicities.[1, 2, 45, 102, 103] These add to the progressive clinical burden in patients with mHSPC, and can result in poor QoL, reduced adherence, and treatment discontinuation.[24, 45, 104-108, 115] There is a clear unmet need for an alternative ARTA + ADT treatment option with improved tolerability to help address these issues.[111] Darolutamide is viewed by APCCC 2024 consensus opinion as a better tolerated treatment option for use in patients with advanced cancer and pre-existing comorbidities, and for older patients.[111] Data from ARANOTE, the pivotal phase III trial evidence in this submission, reporting the safety and efficacy of darolutamide + ADT in mHSPC, suggest darolutamide may have a favourable tolerability profile. In ARANOTE, treatment-emergent adverse events (TEAEs) commonly associated with other ARTAs were generally similar to placebo, low incidences of ARTA-relevant adverse events that may impact patients' daily living were observed, and lower levels of treatment discontinuations due to AEs in the darolutamide vs the placebo arm (discussed in more detail below).[3]

Fatigue is a prevalent and debilitating adverse effect occurring both as a symptom of the disease and as a result of mHSPC treatment, impacting 66–77% of patients.[45] This symptom not only hampers the physical well-being of patients but also significantly affects their mental health, potentially leading to depression and a marked decline in QoL.[80] In younger patients, fatigue reduces work productivity and impacts patient QoL, while in older patients, fatigue is particularly concerning as it may prevent them from receiving treatment intensification, and often necessitates dose modifications or delays.[80]

Fatigue is one of the most frequently occurring adverse events associated with apalutamide and enzalutamide use in advanced prostate cancer, and a key factor influencing the decision not to pursue treatment intensification in England and Wales.[45, 82] Fatigue was found in 19.7% vs 16.7% of apalutamide vs placebo-treated patients in TITAN,[1] and 24.1% vs 19.5% of enzalutamide vs placebo-treated patients in ARCHES,[2] the pivotal phase III trials in patients with mHSPC. Fatigue is a key concern that significantly impacts patient care and treatment outcomes, and is routinely encountered in real-world practice in England and Wales among patients receiving currently available ARTA doublet therapies.[82] ARANOTE is the first study of an ARTA showing a lower rate of fatigue in the treatment group compared with placebo.[3] In ARANOTE, there was a [redacted] lower rate of fatigue in the darolutamide arm vs placebo ([redacted]%).[116] In a survey of expert clinicians conducted at APCCC 2024, a majority would prefer to use darolutamide (44%; 44 votes), compared with apalutamide (7%; 7 votes) and enzalutamide (0%; 0 votes) in patients with advanced prostate cancer with a history of fatigue.[111] Furthermore, clinicians in England and Wales believe the lower levels of fatigue associated with the use of darolutamide could have a substantial positive impact on patients' daily lives.[82]

The distinct chemical structure of darolutamide differentiates it from apalutamide and enzalutamide, and results in reduced BBB penetration and low central nervous system side effects.[45] Both apalutamide and enzalutamide are associated with significant CNS-related AEs. In the ARCHES study, cognitive impairment was found in 4.5% vs 2.1% (All Grades) of enzalutamide vs placebo-treated patients, with Grade ≥3 cognitive impairment in four (0.7%) enzalutamide-treated patients vs no placebo-treated patients.[2] A low exposure-adjusted incidence rate (EAIR) of mental-impairment disorder was observed in ARANOTE for darolutamide vs placebo in both arms ([redacted]).[116] The APCCC 2024 survey found a majority of expert clinicians would prefer to use darolutamide (57%; 57 votes) than either apalutamide (7%; 7 votes) or enzalutamide (0%; 0 votes) in patients with advanced cancer and history of cognitive impairment.[111]

Apalutamide and enzalutamide use has also been associated with seizures. Despite patients with a history of seizures being excluded from participation in TITAN, Grade ≥3 seizure was reported in 0.2% of apalutamide-treated patients.[1] Similarly, Grade ≥3

(serious) seizure was reported in 0.3% of enzalutamide-treated patients in ARCHES, despite patients with a history of seizure being excluded from trial participation.[2] Enzalutamide and apalutamide are thought to induce seizures due to their off-target inhibition of GABA-A receptors,[45] whilst darolutamide has a low binding affinity for GABA-A receptors.[15, 20, 22] The pivotal phase III ARANOTE study did not exclude patients with seizures, yet no increased signal was found.[3, 4, 116] Furthermore, in ARASENS, none of the four patients included in the darolutamide + docetaxel + ADT arm with a history of seizure experienced at TEAE of seizure during the study.[5]

Hypertension is one of the most frequently reported AEs associated with apalutamide and enzalutamide. In ARCHES, hypertension was found in 8.0% vs 5.6% (All Grades) and 3.3% vs 1.7% (Grade ≥3) of enzalutamide vs placebo-treated patients.[2] Exposure-adjusted incidence rates for hypertension in ARANOTE suggest a lower incidence for darolutamide when compared with placebo ([redacted]).[116] Network meta-analyses of ARTA clinical trials have also shown darolutamide to have a low risk of cardiovascular toxicities compared with other ARTAs,[102, 117] and the European Society of Cardiology Guidelines on cardio-oncology reports darolutamide to have the fewest ARTA-related CV toxicities.[118]

Dermatologic toxicities are a significant concern for patients undergoing treatment with apalutamide.[45, 119] These changes can include skin rashes, alterations in nail health, and hair texture or density changes, which not only affect the physical appearance but can lead to considerable psychological and emotional distress.[45, 119, 120] In TITAN, a notable 27.1% vs 8.5% of apalutamide vs placebo-treated patients experienced rash of Any Grade, and 6.3% vs 0.6% had a Grade ≥3 rash.[1] The impact of such dermatologic toxicities on patients is profound. Skin rashes and other related toxicities can significantly diminish a patient's quality of life, contributing to discomfort, itching, and even pain.[120] In England and Wales, expert clinicians have observed that rash due to apalutamide treatment results in significant HCRU.[80] This includes increased visits to healthcare providers, dermatological consultations, and potentially the need for additional medications or treatments to manage these side effects, as well as dose interruptions or discontinuation.[80] Darolutamide serves this key unmet need as it shows no signal for rash in the ARANOTE clinical trial, with an exposure-adjusted incidence rate of [redacted] for both darolutamide and placebo.[116] Results from discrete

choice experiments, including a UK cohort, suggest that patients with mHSPC have a strong preference to avoid treatment-related toxicities, including rash.[51, 121-124]

Apalutamide use is also associated with hypothyroidism, found in 6.5% vs 1.1% of apalutamide vs placebo-treated patients in TITAN.[1] Hypothyroidism is a significant concern with clinicians in England and Wales, as the requirement for thyroid function tests in apalutamide-treated patients adds an additional level of monitoring and complexity to their treatment.[82] No patients were reported in the ARANOTE study to have a TEAE of hypothyroidism,[4, 116] suggesting less management with regards to thyroid disease.

There is also a key need for a prostate cancer agent with improved treatment discontinuation rates due to AEs than apalutamide or enzalutamide (discontinuation rates due to AEs for apalutamide vs placebo: 8.0% vs 5.3% in TITAN[1]; enzalutamide vs placebo: 7.2% vs 5.2% in ARCHES.[2] In ARANOTE discontinuation rates due to adverse events were lower in the darolutamide than the placebo group [redacted]).[116] These findings are consistent with studies of darolutamide + ADT in the nmCRPC setting in ARAMIS,[6, 16] and supported by evidence from a large real-world study (DEAR), which showed a significantly reduced rate of discontinuation for darolutamide compared with enzalutamide and apalutamide.[125] ARANOTE is the only study in mHSPC to show lower discontinuation rates due to AEs in the treatment arm vs the placebo arm and means patients can stay on beneficial treatment for longer.[3]

Use of currently available ARTA-based doublet therapies can lead to DDIs and selecting an ARTA for mHSPC therapy can depend on how it interacts with concomitant medications.[24, 104-108] There are three distinct mechanisms of DDI as follows:

1. ARTAs may compete with comedications for CYP metabolism
2. Induction of CYP enzymes or P-gp may reduce ARTA activity due to faster metabolism
3. Inhibition of CYP enzymes or P-gp may increase ARTA serum concentrations[126-128]

In the complex landscape of anticancer therapy, the interplay between anti-cancer treatments and concomitant medications can significantly impact patient outcomes and HCP time evaluating and monitoring patients. The practice of adjusting medication regimens to avoid adverse DDIs is critical but introduces several challenges in terms of resource use and impact on both healthcare providers and patients. It necessitates a collaborative effort from a whole multidisciplinary team, including general practitioners (GPs), prescribing pharmacists, and oncologists, to ensure safe and effective medication management. This coordination involves extensive crosstalk between these professionals to review patient histories, identify potential interactions, and select the most appropriate alternative medications, correlating to substantial HCRU.

The risk of DDIs is a particular concern in patients with mHSPC, as they are generally elderly with multiple comorbidities requiring concomitant medications.[24, 104-108] Data suggest patients with prostate cancer require a median of 10 concomitant medications (IQR: 7–14; N=1,430).[10] In England, clinicians have reported that real-world management of potential DDIs necessitates the switching of concomitant medications in a significant proportion of patients, ranging from 10–50%, especially among those receiving cardiovascular agents.[80] Cardiovascular disease (CVD) is found in 12.8–33.6% of patients with prostate cancer, with hypertension being the most frequent comorbidity, found in 40.2–63.1% of patients.[9] Apalutamide and enzalutamide are to be avoided, or require dose adjustment or monitoring, when used concomitantly with some of the most commonly prescribed agents for CVD, such as anti-thrombotics, calcium channel blockers and cardiac glycosides, whilst no adjustments are required for darolutamide with these agents.[126-128]

An expert advisory board panel conducted with clinicians practicing in England and Wales stated that hospital pharmacists do not prescribe apalutamide to patients with mHSPC with atrial fibrillation due to risk of DDI .[82] The British Heart Foundation states 1 in 45 people in the UK are living with this condition,[129] and its prevalence increases with age and is higher in men.[130] In a US study of National Inpatient Sample data, the prevalence of atrial fibrillation in patients with prostate cancer positively correlated with age, with the highest rate found in the group of patients aged ≥75 years (32.8%; data

from 2017).[131] In ARANOTE, findings of atrial fibrillation were low for both the darolutamide and the placebo arm, with an EAIR of 0.9 and 0.6, respectively.[116]

Table 3 summarises potential DDIs associated with the second generation ARTAs. Overall, the British National Formulary (BNF) lists as many as 310 potential DDIs for apalutamide, 233 for enzalutamide, and 43 for darolutamide (accessed April 2025).[11, 12, 23] A DDI of key concern is apalutamide's interaction with relugolix, a new ADT therapy, and the first oral ADT to market.[14] ARTA therapy is required to be administered in combination with ADT for the treatment of mHSPC,[127, 128] and the BNF lists apalutamide use is to be avoided or dose adjusted with relugolix.[13] Furthermore, manufacturer's guidance states that co-administration of relugolix with apalutamide is not recommended, as apalutamide is a combined P-gp and strong CYP3A4 inducer.[14]

Table 3: Summary of interactions between ARTA and other medicinal products

Examples	Interaction types	darolutamide	enzalutamide	apalutamide
Analgesics				
Fentanyl	CYP3A4 substrate		Adjust/monitor[a]	Adjust/monitor
Antibiotics/antifungals				
Clarithromycin	Inhibitor of P-gp; CYP3A4; OATP1B1 and OATP1B3	Avoid[b]	Adjust/monitor	Adjust/monitor
Itraconazole	Inhibitor of CYP3A4	Avoid		
Ketoconazole	Inhibitor of CYP3A4	Avoid		
Rifampicin	Inducer of P-gp; CYP3A4, A2, 2B6, 2C9, 2C19; OATP1B1 and OATP1B3	Avoid	Adjust/monitor	Adjust/monitor
Anticonvulsants				
Carbamezepine	Inducer of P-gp; CYP3A4; OATP1B1 and OATP1B3	Avoid	Adjust/monitor	Adjust/monitor
Antipsychotics				
Haloperidol	Substrate of CYP3A4 and CYP2D6; CYP2D6 inhibitor	Adjust/monitor	Adjust/monitor	Adjust/monitor
Quetiapine	CYP3A4 substrate		Adjust/monitor	Adjust/monitor
Antithrombotics				
Warfarin	CYP2C9-substrate		Avoid	Avoid

Examples	Interaction types	darolutamide	enzalutamide	apalutamide
Clopidogrel	Inhibitor of CYP2C8, CYP2B6, and OATP1B1		Adjust/monitor	Adjust/monitor
Dabigatran	P-gp substrate		Adjust/monitor	Adjust/monitor
Rivaroxaban	CYP3A4-substrate		Adjust/monitor	Adjust/monitor
Calcium channel blockers				
Felodipine	CYP3A4-substrate		Adjust/monitor	Adjust/monitor
Verapamil	Inhibitor of CYP3A4 (moderate) and P-gp; P-gp substrate		Adjust/monitor	
Diltiazem	Inhibitor of CYP3A4		Adjust/monitor	Adjust/monitor
Amlodipine	CYP3A4-substrate		Adjust/monitor	Adjust/monitor
Cardiac glycosides				
Digoxin	P-gp substrate		Adjust/monitor	Adjust/monitor
Hypnotics				
Diazepam	CYP2C19 substrate		Adjust/monitor	Adjust/monitor
Midazolam	CYP3A4 substrate	Adjust/monitor	Adjust/monitor	Adjust/monitor
Proton pump inhibitors				
Omeprazole	CYP2C19 substrate; CYP2C19 inhibitor		Adjust/monitor	Adjust/monitor
Statins				
Rosuvastatin	Substrate of BCRP, OATP1B1 and OATP1B3	Avoid		Adjust/monitor
Fluvastatin	Substrate of BCRP, OATP1B1 and OATP1B3	Adjust/monitor		Adjust/monitor
Atorvastatin	Substrate of BCRP, OATP1B1 and OATP1B3	Adjust/monitor	Adjust/monitor	Adjust/monitor
Simvastatin	Substrate of BCRP, OATP1B1 and OATP1B3	Adjust/monitor	Adjust/monitor	Adjust/monitor
LHRH antagonists				
Relugolix (oral administration)	P-gp and strong CYP3A inducer			Avoid

[a]SmPC lists interaction as cause for adjustment or monitoring. [b]SmPC lists as a cause for avoiding coadministration.

Abbreviations: BCRP: breast cancer resistance protein; CYP: cytochrome P450; LHRH: luteinizing hormone releasing hormone; OATP: organic anion-transporting polypeptide; P-gp: P-glycoprotein 1.

Sources: SmPC darolutamide[126]; SmPC apalutamide[127]; SmPC enzalutamide.[128]

A review of safety differences across ARTAs in nmCRPC highlighted the significant HCRU burden resulting from potential DDIs and the downstream effects on treatment plans, clinical outcomes and patient quality of life. The study suggested that, in

addition to weighing the treatment-emergent adverse events and DDIs, the full cascade of potentially avoidable healthcare complications should be assessed to when selecting the best ARTA to optimise therapy for the patient.[132] Treatments associated with fewer DDIs and treatment emergent effects, such as darolutamide, are likely to be crucial to the optimisation of HCRU, efficient patient management and optimal patient outcomes.

In summary, the reimbursement of darolutamide + ADT will address important unmet needs affecting the current mHSPC treatment landscape and offer an additional treatment option to apalutamide for patients with mHSPC who are ineligible to receive treatment with docetaxel. Clinicians in England and Wales confirm that darolutamide's differentiated tolerability and low potential for DDI's, may simplify treatment management for physicians and patients.[80, 82] Darolutamide's differentiated tolerability opens the possibility of treatment intensification to patients of older age, and/or living with comorbidities and at potential risks of DDIs that make them ineligible for currently available treatments, and thus address current issues of inequity in treatment for mHSPC.[72, 80, 82]

B.1.4 Equality considerations

The currently available ARTA treatment options for mHSPC are not recommended for patients with a history of seizures or other predisposing factors, and these patients were excluded from the pivotal trials (TITAN and ARCHES, respectively). In clinical practice, the only treatment option for these patients is ADT monotherapy, which is considered suboptimal compared to treatment intensification with ARTA-based triplet or doublet therapy.[58, 61] Clinicians in England and Wales stated this exclusion highlights a small but significant equality gap in the treatment pathway, leaving an underrepresented group of patients without effective treatment options.[82] Darolutamide addresses this unmet need given that there is no use restriction in patients with a history of seizure.[126] In the ARANOTE study, people with seizure were eligible for inclusion, and one patient with seizure history participated in the trial.[3, 4]

Health inequalities affect the burden of mHSPC, particularly in subpopulations such as Black males, who have a higher incidence of prostate cancer than White males (1 in 4 vs 1 in 8 men, respectively) and a higher PC-specific mortality rate (approximately

2.1 times higher). [27, 54, 133-135] The National Prostate Cancer Audit (NCPA) has highlighted the need for equitable access to newer prostate cancer therapies across the UK.[101] There is a particular unmet need for additional treatments for patients of older age, or who are frail or have comorbidities. Evidence suggests the use of treatment intensification decreases in these patients, as well as among Black patients and those subject to socioeconomic deprivation.[72] A recent national population study in England found significant under-use in older patients, with only 16.8% (n=2404) of men aged ≥75 years having a record of treatment intensification vs 59.8% (n=9184) of those aged <75 years.[72]

B.2 Key drivers of the cost effectiveness of the comparator(s)

B.2.1 Clinical outcomes and measures

The previous technology appraisal for apalutamide (TA741) in mHSPC is of interest to this appraisal. [84] Relevant outcome measures identified in TA741 that were used to estimate cost-effectiveness for mHSPC included radiographic progression-free survival (rPFS), overall survival (OS), second progression-free survival (PFS2), safety, and HRQoL.[84] The definitions of rPFS, OS and PFS2 are included below.

- rPFS was defined as the time from randomisation to first imaging-based documentation of progressive disease or death, whichever occurred first
- OS was defined as the time from randomisation to the date of death from any cause
- PFS2 was defined as the time from randomisation to first occurrence of investigator-determined disease progression (prostate-specific antigen progression, progression on imaging, or clinical progression) while patient was receiving first subsequent therapy for prostate cancer, or death due to any cause, whichever occurs first.

Comparative effectiveness data for apalutamide + ADT and placebo + ADT were derived directly from the TITAN study.[69] The clinical outcomes and measures appraised in TA741 are presented in Table 4. One-way sensitivity analysis did not include the clinical effectiveness parameters (rPFS, OS and PFS2). Therefore, the results from the scenario analyses were reviewed and indicated the alternative distributions for rPFS has a moderate impact on the incremental cost-effectiveness ratio (ICER), while the impact of other outcomes on the ICER was minimal or negligible (Table 4).[84 136]

Table 4: Clinical outcomes and measures appraised in TA741 for apalutamide for treating metastatic hormone-sensitive prostate cancer (mHSPC)[84, 136]

Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER*	Committee's preferred assumptions	Uncertainties impacting the ICER
rPFS	Months (median) Hazard ratio	Yes	Moderate increase	The company chose Weibull distributions based on the clinical advice and decided to fit parametric curves to both arms independently. However, the ERG noted the immaturity of the apalutamide plus ADT data, which is a large driver of the cost-effectiveness results. They also observed that Weibull models had worse statistical fit compared to other models. Expert advice suggested the Weibull models might underestimate progression in the ADT arm over time, recommending more flexible models. The committee agreed that, because of the uncertainty with the Weibull model, it would have liked a more flexible model fitted to extrapolate rPFS beyond the duration of TITAN. At consultation, the company declined to explore flexible approaches. It said that these might be more uncertain than standard parametric models, because of their complexity and number of assumptions. It also said that a flexible approach needed a clinical or statistical reason to justify the time point at which the curves flex, which it considered did not exist. The committee concluded that the company's approach to extrapolating rPFS was uncertain, which the committee factored into its decision making.	Uncertainty remained over appropriate method of extrapolation

Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER*	Committee's preferred assumptions	Uncertainties impacting the ICER
OS	Months (median) Hazard ratio	Yes	Minimal	Independently modelled with Weibull distributions based on 'informed fits' approach, not adjusted for novel therapy restriction. The committee concluded that, although it would have liked to have seen flexible models explored, the Weibull model was acceptable for decision making.	None
PFS2	Months (median) Hazard ratio	Yes	Minimal	The company, having assessed that the proportional hazards assumption holds for PFS2, applied a Weibull model jointly to both treatments in its base case, based on clinical plausibility and consistency with rPFS and OS. The ERG noted that both the Weibull and Gompertz models have the best statistical fits to the observed data. However, the Weibull model likely overestimates PFS2 at 10 and 15 years for people who have apalutamide plus ADT. Also, the ERG stated that the model appears to predict that people spend almost no time on the third-line treatment for metastatic disease. The ERG considered that the Gompertz model was the only clinically relevant alternative, although it is also likely to overestimate long-term survival for people who have apalutamide plus ADT. The ERG noted that, because the PFS2 estimates were immature in TITAN, extrapolating PFS2 assuming proportional hazards was likely to be highly uncertain. The ERG suggested that more flexible approaches would be appropriate. The committee concluded that the true estimates of PFS2 after the end of the trial were	None

Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER*	Committee's preferred assumptions	Uncertainties impacting the ICER
				uncertain because these were based on immature data.	
HRQoL	Utilities	Yes	Minimal decrease	Utility values used for pre-progression and post-progression (1L mHRPC) are taken from TITAN. Utility values from TA377 without any adjustment were used for the second-line and third-line mHRPC.	None
Safety	Percentages	Yes	None	Based on Grade 3-4 treatment related adverse event rates from TITAN, with associated costs from literature.	None

[a]Was the ICER sensitive to changes in this outcome? How did changes in the outcome affect the ICER (increase or decrease)?
Abbreviations: ADT: androgen deprivation therapy; HRQoL: Health related quality of life; ICER: Incremental cost-effectiveness ratio; mHRPC: metastatic hormone-relapsed prostate cancer; PFS: progression-free survival; rPFS: radiographic progression-free survival; OS: overall survival.

B.2.2 Resource use assumptions

The key resource use assumptions made in the submission for apalutamide (TA741) are summarised in Table 5.[84] The committee's and ERG's preferred assumptions are indicated where the original assumption was contested.

Table 5: Key resource use assumptions in TA741 for apalutamide for treating metastatic hormone-sensitive prostate cancer (mHSPC)[1]

Assumption	Assumption description	Committee and ERG preferred assumption
Subsequent treatments	The subsequent therapies consist of abiraterone, enzalutamide, BSC, docetaxel, cabazitaxel and radium223. The proportion of patients receiving subsequent treatments is estimated from the company's mHSPC advisory board.	The ERG notes that patients with mHSPC treated with ADT alone received docetaxel as a subsequent treatment. This is inappropriate for the company's analyses for people ineligible/unsuitable for docetaxel in mHSPC, as by definition, they are not able to receive docetaxel. Due to the low cost of docetaxel, this is unlikely to have a large impact on the model results.
Health state unit costs	Patients treated with apalutamide would receive prostate-specific antigen and other blood tests every 12 weeks.	ERG suggests minor differences to the frequency of investigations for mHSPC, patients treated with apalutamide would receive prostate-specific antigen and other blood tests every 4 weeks for the first 3 months (rather than every 12 weeks) and then every 12 weeks thereafter.

Abbreviations: ADT: androgen deprivation therapy; BSC: Best supportive care; ERG: Evidence Review Group; mHSPC: metastatic hormone-sensitive prostate cancer.

B.3 Clinical effectiveness

Summary*

- The pivotal phase III trials ARANOTE[3] (darolutamide + ADT in mHSPC) and TITAN (apalutamide + ADT in mHSPC) are the RCTs relevant to this decision problem.[1] ARANOTE provides clinical data for darolutamide, whilst darolutamide data are compared with apalutamide data from TITAN through indirect treatment comparison.
- ARANOTE is a global, randomised, double-blind, placebo-controlled phase III trial conducted in participants with mHSPC (n=669) to compare darolutamide (600 mg twice daily) + ADT (n=446) to placebo + ADT (n=223).
- Baseline characteristics and demographics were similar and well-balanced between treatment arms in ARANOTE, with a diverse patient population reflective of the UK population in the real world.[3, 4, 80]
- At primary completion analysis (data cut-off (DCO): Jun 7, 2024), ARANOTE met its primary endpoint, showing darolutamide + ADT significantly reduced the risk of rPFS or death by 46% (HR, 0.54; 95% CI, 0.41–0.71; p<0.001) when compared with placebo + ADT in patients with mHSPC, with a consistent benefit across all pre-planned subgroups.[3]
- At final OS analysis (DCO: [redacted]), there was a [redacted] darolutamide + ADT for OS (HR: [redacted] one-sided [redacted]) vs placebo + ADT, and clinical benefit was clear and consistently seen across all pre-specified subgroups, with HRs <1.0.[116]
- Darolutamide + ADT delayed the time to mCRPC by 60% when (HR, 0.40; 95% CI, 0.32–0.51) and time to pain progression by 28% (HR, 0.72; 95% CI, 0.54–0.96) when compared with placebo + ADT in ARANOTE.[3]
- A smaller percentage of patients in the darolutamide vs placebo arm progressed to mCRPC (34.5% vs 64.1%) or had pain progression (27.8% vs 35.4%) in ARANOTE.[3]

- Deep and durable PSA responses similar to ARASENS[89] were found in ARANOTE, with PSA undetectable (<0.2 ng/ml at any time during treatment) in 62.6% vs 18.5% of darolutamide-treated patients, and a 69% reduction (HR, 0.31; 95% CI, 0.23–0.41) in time to PSA progression.[3]
- Patient-relevant HRQoL benefit (BPI-SF) was observed in ARANOTE for darolutamide + ADT vs placebo + ADT.[3]
- Time to initiation of subsequent systemic anticancer therapy was significantly delayed in the darolutamide arm compared with the placebo arm (HR, 0.40; 95% CI, 0.29 to 0.56; p<0.0001) in ARANOTE.[3]
- Expert clinicians have expressed confidence in prescribing darolutamide + ADT to patients with mHSPC based on the comprehensive body of supportive evidence from the ARANOTE, ARASENS and ARAMIS trials which demonstrate clinically meaningful survival benefits for darolutamide in prostate cancer across all studies.[3, 16, 89, 137]
- Results from an NMA comparing darolutamide + ADT with apalutamide + ADT on OS and rPFS found no difference in OS or rPFS between darolutamide + ADT and apalutamide + ADT.

*The primary endpoint rPFS and all secondary endpoints (other than OS) are from the primary completion analysis DCO Jun 7, 2024; OS and safety data presented are from the final OS analysis DCO [redacted].

B.3.1 Identification and selection of relevant studies

Full details of the systematic literature review process and methods used to identify and select the clinical evidence relevant to this appraisal are provided in Appendix D. Briefly, searches for the SLR were originally conducted on 18 October 2021 and updated on 26 May 2022, 12 December 2023, and 24 October 2024. Across the original SLR and three subsequent updates, a total of 400 reports related to 42 unique clinical studies were eligible for inclusion in the SLR. Only two randomised clinical trials (RCTs) were identified as being relevant to this decision problem: the pivotal phase III trials ARANOTE[3] (darolutamide + ADT in mHSPC) and TITAN (apalutamide + ADT in mHSPC).[1] ARANOTE provides clinical data for darolutamide, whilst darolutamide data are compared with apalutamide data from TITAN through indirect treatment comparison.

B.3.2 List of relevant clinical effectiveness evidence

The pivotal phase III ARANOTE study is summarised in Table 6.

Table 6: Clinical effectiveness evidence

Study	ARANOTE (NCT04736199; Clinical Study Report date: September 2024)
Study design	ARANOTE is a global, phase III, double-blind trial designed to assess the efficacy and safety of darolutamide + ADT compared to placebo + ADT in patients with mHSPC [3, 4]
Population	Adult men with mHSPC
Intervention(s)	Darolutamide with ADT
Comparator(s)	Placebo with ADT
Indicate if study supports application for marketing authorisation	Yes
Reported outcomes specified in the decision problem	• Radiographic progression free survival • Overall survival • Time to castration resistant prostate cancer • Time to initiation of subsequent anti-cancer therapy • PSA undetectable rate (<0.2 ng/ml) • Time to prostate-specific antigen progression • Adverse effects of treatment • Time to pain progression (BPI-SF) • Health-related quality of life.
All other reported outcomes	• Detectable PSA rate (≥0.2 ng/ml)

Abbreviations: ADT: androgen deprivation therapy; mHSPC: metastatic hormone-sensitive prostate cancer; OS: overall survival; rPFS: radiological progression-free survival

Sources: ARANOTE Clinical Study Report September 2024, Bayer AG[4]; Saad et al., 2024.[3]

B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

B.3.3.1 Study design

A summary of the ARANOTE trial methodology is provided in Table 7. Briefly, ARANOTE is a global, randomised, double-blind, placebo-controlled phase III trial conducted in participants with mHSPC to compare darolutamide + ADT to placebo +

ADT. The study was conducted in 133 sites in 15 countries across Asia, Latin America, Europe, Australia, New Zealand, Canada, and South Africa.[3, 4]

The study had broad eligibility criteria and enrolled a diverse population representative of current real-world patients with mHSPC. Key inclusion and exclusion criteria are summarised in Table 7. Adults aged 18 years and older were eligible if they had confirmed metastatic adenocarcinoma of the prostate. Eligible patients had an ECOG performance status of 0–2; had adequate bone marrow, liver, and renal function; and started on ADT with/without a first-generation anti-androgen within 12 weeks of randomisation. The study included patients with *de novo* and recurrent disease. Patients with a history of seizures, who can be more difficult to treat, were eligible for study inclusion. Patients were excluded if they had regional lymph node metastases only, had a baseline superscan, had received androgen receptor pathway inhibitors or chemotherapy for prostate cancer, or radiotherapy in the 2 weeks prior to randomisation.[3, 4]

Prespecified subgroups were age, race, geographic region, renal or hepatic function at baseline, ECOG PS at baseline, baseline PSA, Gleason score, and high- and low-volume disease. Subgroups based on disease volume were defined according to CHAARTED,[113] with high-volume disease defined by the presence of visceral metastases and/or at least four bone lesions, with at least one beyond the vertebral bodies and pelvis. Patients were also stratified by use of prior local therapy, or local radiotherapy or prostatectomy.[3, 4]

All patients (n=669) started ADT of investigator choice within 12 weeks before initiating study treatment. Investigator/study site personnel, sponsor, and patients were blinded to the treatment interventions. Patients were randomised in a 2:1 ratio using an interactive web response system (IWRS) to receive darolutamide 600 mg twice daily (n=446) or matched placebo (n=223). All patients received study drug until radiological disease progression, unacceptable toxicity, initiation of new anticancer therapy, patient or physician decision, or study drug interruption of more than 28 consecutive days.[3, 4]

During the treatment phase and active follow-up (after discontinuation of study drug), patients were evaluated at clinic visits every 12 weeks. Active follow-up continued for approximately 1 year (12±1 months). Participants then entered the long-term (survival) follow-up period where they were contacted by telephone approximately every 12 weeks.

The primary endpoint was rPFS, defined as the time from randomisation to the first documentation of radiological progressive disease in soft tissue or bone, or death due to any cause, based on central review of conventional imaging, and using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 for soft tissue metastases[138] and Prostate Cancer Working Group 3 (PCWG3) criteria for bone metastases (Table 7).[4, 28]

Secondary efficacy endpoints (pre-specified) were OS, time to initiation of subsequent systemic anticancer therapy for prostate cancer, time to CRPC, time to PSA progression, rates of PSA <0.2 ng/mL in patients with baseline PSA ≥2 ng/mL and time to pain progression (Table 7). Adverse events were assessed from the first dose of study drug until 30 days after the last treatment and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0. An independent data monitoring committee reviewed unblinded safety data throughout the study.[3, 4]

Additional pre-specified endpoints included PFS2 assessed by the investigator, time to symptomatic skeletal event (SSE), time to deterioration in FACT-P total score and time to first prostate cancer-related invasive procedure.[4]

Table 7: ARANOTE trial methodology summary

Study ID/name	ARANOTE (NCT04736199)
Location	133 sites in 15 countries across Asia, Latin America, Europe, Australia, New Zealand, Canada, and South Africa
Study design	Randomised, double-blind, placebo-controlled, phase III study
Duration	The trial consists of 4 phases: • **Screening**: Participant screening occurred within 28 days prior to randomisation • **Treatment**: First administration of drug until radiologically confirmed disease progression

Study ID/name	ARANOTE (NCT04736199)
	• **Active follow-up**: SoC clinic visits every 12 weeks for 12 ± 1 months • **Long-term (survival) follow-up**: After active follow-up period, patients entered long-term follow-up with contact every 12 weeks until death, loss to follow-up, withdrawal of consent, or end-of-study
Treatment group(s)	Patients (n=669) randomised 2:1 to receive darolutamide (n=446) or placebo (n=223)
Dosing regimen	Darolutamide 600 mg (2 tablets of 300 mg) BID with food, equivalent to a total daily dose of 1200 mg or Placebo darolutamide matched tablets in appearance, BID with food.
Concomitant medications	• All participants must receive ADT of investigator's choice (LHRH agonist/antagonists or orchiectomy) as standard therapy, on a continuous basis
Key inclusion criteria	• Males aged 18 years • Histologically or cytologically confirmed adenocarcinoma of the prostate • Documented metastatic disease centrally confirmed by conventional imaging method • Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 • Started ADT (LHRH agonist/antagonist or orchiectomy) with or without first-generation anti-androgen (≤12 weeks before randomisation) • Adequate bone marrow, liver, and renal function • Included both de novo and recurrent disease
Key exclusion criteria	• Regional lymph node metastases only (N1, below the aortic bifurcation) • Baseline superscan • Prior treatment with: o LHRH agonist or antagonist started >12 weeks before study treatment starts except neoadjuvant and/or adjuvant therapy for a duration of ≤24 months and completed ≥12 months prior to randomisation o Second-generation ARIs or other investigational ARIs o CYP17 enzyme inhibitors as antineoplastic treatment o Chemotherapy (docetaxel or immunotherapy for PC) o Radiotherapy in the 2 weeks prior to randomisation
Primary endpoint	• rPFS defined as time from date of randomisation to date of progressive disease (PD) in malignant soft tissue lesions, PD in malignant bone lesions, or death due to any cause, whichever occurred first as assessed by BICR based on RECIST v.1.1

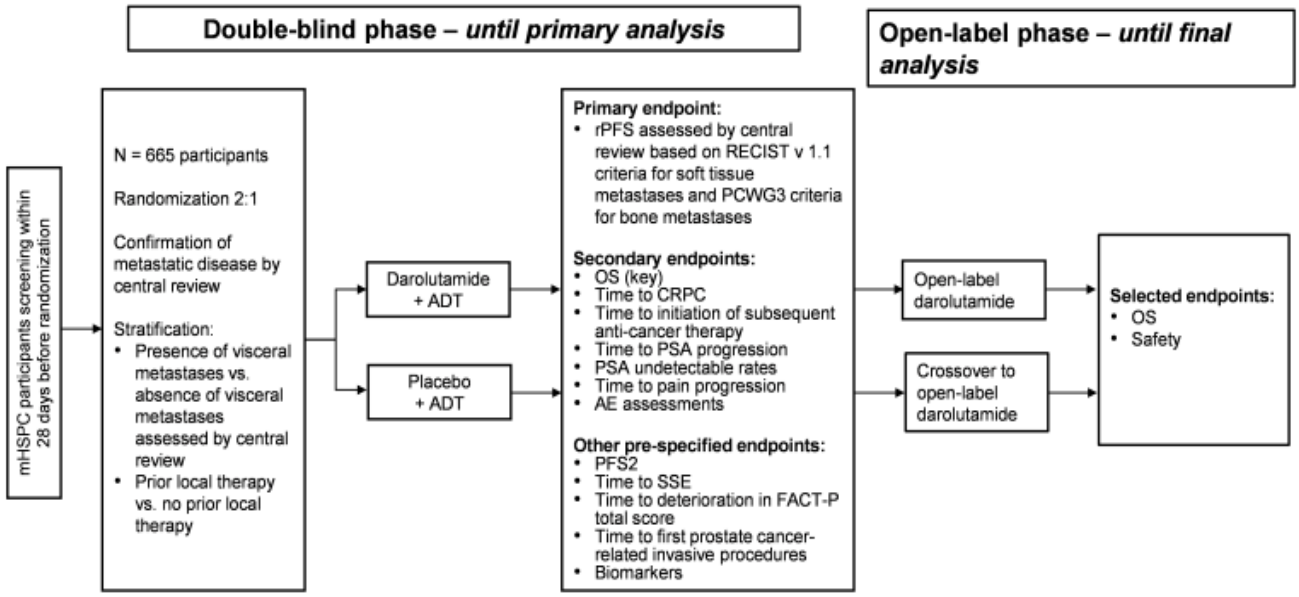
Study ID/name	ARANOTE (NCT04736199)
	criteria for malignant soft tissue lesions[138] and PCWG3 criteria for malignant bone lesions.[28]
Secondary endpoint(s)	• OS (key secondary endpoint) defined as the time from randomisation to the date of death from any cause. • Time to CRPC defined as time from randomisation to PSA progression or radiological progression by malignant soft tissue lesions or bone lesions or occurrence of SSE. • Time to initiation of subsequent anticancer therapy (from randomisation). • Time to PSA progression (from randomisation) • PSA undetectable rates (<0.2 ng/mL) assessed centrally, defined as the percentage with detectable PSA values (≥0.2 ng/mL) at baseline, that became undetectable (<0.2 ng/mL) between randomisation and 30 days after the last dose of study drug or start of a new anticancer therapy. • Time to first pain progression (from randomisation) assessed by Q3 of the BPI-SF questionnaire related to the worst pain in the last 24 hours (WPS) taken as an average for postbaseline score, and/or initiation of short or long-acting opioids for malignant disease for ≥7 consecutive days after randomisation. Initiation or change in the use of other non-opioid analgesics was not used in the assessment of pain progression. • AE assessments using NCI-CTCAE (v. 5.0).
Study initiation date	23 February 2021 (first patient first visit)
Primary completion date	7 June 2024
Data-base lock date	3 July 2024
Date of final OS analysis	[redacted]

Abbreviations: ADT: androgen deprivation therapy; AE: adverse event; BICR: Blinded independent central review; BPI-SF: Brief Pain Inventory – Short Form; CRPC: castration-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; NCI-CTCAE (v. 5.0): National Cancer Institute–Common Terminology Criteria for Adverse Events (version 5.0); OS: overall survival; PCWG3: Prostate Cancer Working Group 3; PSA: prostate-specific antigen; RECIST v. 1.1: Response Evaluation Criteria in Solid Tumors version 1.1; rPFS: radiological progression-free survival; SSE: Symptomatic skeletal event; WPS: Worst pain subscale.

Sources: ARANOTE Clinical Study Report September 2024, Bayer AG[4]; Saad et al., 2024[3] ARANOTE Final Overall Survival Results [redacted], Bayer AG.[116]

The study design schematic is presented in Figure 2.

Figure 2: ARANOTE study design schematic



Abbreviations: ADT: Androgen deprivation therapy; AE: Adverse event; CRPC: Castration-resistant prostate cancer; FACT-P: Functional Assessment of Cancer Therapy-Prostate; mHSPC: Metastatic hormone-sensitive prostate cancer; OS: Overall survival; PCWG3: Prostate Cancer Working Group 3; PFS2: Progression-free survival 2; PSA: Prostate-specific antigen; RECIST: Response Evaluation Criteria in Solid Tumors; rPFS: Radiological progression-free survival; SSE: Symptomatic skeletal event

Sources: ARANOTE Clinical Study Report September 2024, Bayer AG[4]; Saad et al., 2024.[3]

B.3.3.2 Baseline demographics

Patient demographics and baseline characteristics of patients included in the ARANOTE study are summarised in Table 8. Baseline characteristics and demographics were similar and well-balanced between treatment arms. The median age (range) of patients was 70 (43–93) years. Median PSA at baseline was 21.3 ng/mL (following ADT initiation within the previous 12 weeks) and similar in each treatment arm.[3, 4] Use of concomitant medications was generally well-balanced between the treatment arms (93.5% of participants in the darolutamide arm and 91.0% in the placebo arm.[4]

ARANOTE included a diverse patient population representative of real-world patients with mHSPC, with a wide representation of races and ethnicities that are reflective of the UK population in the real world.[3, 4, 80] A total of 31.2% of patients were Asian and 9.7% were Black. Racial diversity was well-balanced between treatment arms.[3, 4]

All patients had metastatic disease at study entry and a majority had received no prior local therapy (82.1%). An ECOG performance status (PS) of 0 or 1 was found in 49.8% and 47.2% of patients; whilst 3.0% had an ECOG PS 2. It is important to note, the study included a significant proportion of patients with high Gleason scores of ≥8 (68.3%), 72.5% of patients with *de novo* disease and 70% had high-volume disease, all indicative of more advanced disease. A total of 12.0% of patients had visceral metastases by central review.[4]

Table 8: Patient demographic and clinical characteristics at baseline (full analysis set; FAS)

		Darolutamide + ADT (N=446)	Placebo + ADT (N=223)
Age, median (range), years		70 (43-93)	70 (45-91)
Age group, year, n (%)	<65	118 (26.5)	65 (29.1)
	65–74	193 (43.3)	96 (43.0)
	75–84	117 (26.2)	52 (23.3)
	≥85	18 (4.0)	10 (4.5)
Race, n (%)	White	251 (56.3)	125 (56.1)
	Asian	144 (32.3)	65 (29.1)
	Black	41 (9.2)	24 (10.8)
	Other	10 (2.2)	9 (4.0)
Region, n (%)	Asia	141 (31.6)	63 (28.3)
	Latin America	119 (26.7)	72 (32.3)
	Europe, Rest of World	186 (41.7)	88 (39.5)
EGOG PS, n (%)	0	235 (52.7)	98 (43.9)
	1	199 (44.6%)	117 (52.5)
	2	12 (2.7)	8 (3.6)
Gleason score at initial diagnosis, n (%)	<8	122 (27.4)	67 (30.0)
	≥8	311 (69.7)	146 (65.5)
	Data missing	13 (2.9)	10 (4.5)

Serum PSA, median (range), ng/mL		21.4 (0.02-15,915)	21.2 (0.02-8,533)
Median alkaline phosphatase level (range) — U/L		132.7 (34–4,286)	147.0 (36–3,764)
Metastases at initial diagnosis, n (%)[a]	*De novo*	317 (71.1)	168 (75.3)
	Recurrent	100 (22.4)	45 (20.2)
	Unknown	29 (6.5)	10 (4.5
Extent of metastatic disease stage at screening, n (%)	Nonregional lymph node only	17 (3.8)	10 (4.5)
	Bone metastases with or /without lymph node	344 (77.1)	171 (76.7)
	Visceral metastases with or /without bone or lymph node	85 (19.1)	42 (18.8)
Disease volume, n (%)[b]	High	315 (70.6)	157 (70.4)
	Low	131 (29.4)	66 (29.6)
Random assignment stratification factors			
Visceral metastases, n (%)[c]	Yes	53 (11.9)	27 (12.1)
	No	393 (88.1)	196 (87.9)
Prior local therapy, n (%)	Yes	80 (17.9)	40 (17.9)
	No	366 (82.1)	183 (82.1)

[a]Recurrent disease is defined as stage I to IVA and de novo is defined as stage IVB at initial diagnosis. [b]Disease volume defined by CHAARTED criteria: presence of visceral metastases and/or ≥4 bone metastases with ≥1 beyond vertebral bodies and pelvis.[113] [c]Centrally assessed.

Abbreviations: ADT: androgen deprivation therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Score; PSA: prostate specific antigen.

Source: Saad et al, 2024.[3]

B.3.3.3 Method of expert elicitation

Expert opinion for this submission was obtained from two advisory board meetings. The first took place on 6 December 2024 to understand treatment practices for mHSPC in the UK, and to gain feedback on ARANOTE data and its relevance to UK clinical practice.[80] The second advisory board focused on HEOR topics to validate NICE submission approach.[82] Clinical experts attending these panels were identified by the Bayer medical team and selected based on their expertise in treating patients with advanced prostate cancer. Furthermore, they were chosen from different regions across England to give full representation across different health boards.

B.3.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The predefined analysis populations used to analyse the ARANOTE trial data (FAS and safety populations) are defined in Table 9.

Table 9: Populations for analyses

Population	Description
Enrolled	All participants who signed the informed consent form
FAS	All participants randomised, grouped according to their allocated treatment at randomisation, irrespective of the actual treatment received
SAF	All participants randomised who took ≥1 dose of study drug. Participants were analysed according to the study drug they received.

Abbreviations: FAS: Full analysis set; SAF: Safety analysis set
Source: ARANOTE Clinical Study Report September 2024, Bayer AG.[4]

A summary of statistical analyses methodology applied in ARANOTE is shown in Table 10.

Table 10: Summary of statistical analyses

Trial number (acronym)	Hypothesis objective*	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
NCT04736199 (ARANOTE)	The primary objective of the study was to determine if darolutamide in addition to ADT is superior to placebo plus ADT by improving rPFS in participants with mHSPC. The null hypothesis that there is no difference in rPFS between the treatment arms (equivalent to a hazard ratio [HR] of 1) was tested against the alternative hypothesis that the HR of darolutamide over placebo is <1.	The full analysis set (FAS) was analysed for rPFS using a stratified log-rank test with the randomisation stratification factors (visceral metastases and prior local therapy). The Cox regression model was used to determine stratified HRs and 95% CIs for the treatment comparison, and Kaplan–Meier estimates presented rPFS at various time points with 95% CIs for both groups. Subgroup analyses of rPFS and OS were performed to determine the effect of demographic and baseline characteristics using an unstratified Cox regression model. Secondary efficacy endpoints were to be tested for statistical significance using a hierarchical gatekeeping procedure only if the primary endpoint was statistically significant (two-sided alpha of 0.05) using the same alpha in the following order: OS, time to initiation of subsequent systemic anticancer therapy, time to CRPC, time to PSA progression, rates of PSA <2 ng/mL, and time to pain progression. Secondary time-to-event endpoints were analysed in a similar manner as the primary endpoint, while rates of PSA <0.2 ng/mL were compared between treatment groups using a stratified Cochran–Mantel–Haenszel test. An interim analysis of OS was conducted at the time of the primary rPFS analysis; final analysis of OS is planned when approximately 180 events have occurred. The stopping boundaries for these two survival analyses will be calculated with an O'Brien–Fleming alpha-spending function based on the actual number of survival events observed up to the primary data cutoff date and the expected OS at final analysis. Descriptive statistics were used to summarise demographic and baseline characteristics, rates of PSA < 0.2 ng/mL, and adverse events by treatment group. Statistical evaluations were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA).	Sample size calculations were based on determining a difference in the primary endpoint (rPFS) between the darolutamide and placebo groups. Approximately 665 patients were required to observe 214 progression events, allowing for a 33% dropout rate for rPFS follow-up, and to provide the trial with 90% power using a two-sided alpha of 0.05 with an HR of 0.625 for rPFS.	Patients who withdraw from study treatment participated in follow-up, unless consent was withdrawn Missing data was not estimated or carried forward in any statistical analysis except for: 1. Partially missing start date or end date of study. 2. Time-to-event endpoints missing day but not month or year that could be imputed as day 15 of the month. 3. Brief Pain Inventory – Short form (BPI-SF), pain interference score was set to missing if ≥4 of 7 is missing, while pain severity score was set to missing if ≥1 of 4 scores is missing. 4. If ≤50% of FACT-P subscales were answered the score was set to missing.

Abbreviations: BPI-SF: Brief Pain Inventory – Short Form; CI: confidence interval; CRPC: Castration-resistant prostate cancer; FACT-P; Functional Assessment of Cancer Therapy-Prostate; HR: hazard ratio; OS: Overall survival; PSA: Prostate-specific antigen; rPFS: Radiological progression-free survival.

Source: ARANOTE Clinical Study Report September 2024, Bayer AG[4]; Saad et al., 2024.[3]

B.3.5 Critical appraisal of the relevant clinical effectiveness evidence

A quality assessment of the ARANOTE study was conducted using the NICE checklist. A summary is presented in Table 11. The study was approved by the institutional review board and independent ethics committee and was conducted according to good clinical practice. Overall, the study is methodologically robust and of high-quality with a comprehensive approach to patient allocation, control of confounding factors, and an overall low risk of bias.

Patients were randomised to receive darolutamide or matching placebo in a double-blind fashion, such that neither the investigator, the sponsor nor the patient knew which agent was being administered. All efficacy and safety parameters, and the methods to measure them, are standard variables and methods used in clinical studies and/or clinical practice. They are widely used and generally recognised as reliable, accurate and relevant.

Table 11: Quality assessment results for RCTs

	ARANOTE
Was randomisation carried out appropriately?	Yes. Randomisation was appropriate and carried out centrally using an Interactive Web Response System (IWRS) system.
Was the concealment of treatment allocation adequate?	Yes. The study was double-blinded such that neither the investigator or study site personnel, the study sponsor or participant knew which drug was being administered. The appearance of darolutamide and placebo were identical, and study drugs were packed in bottles labelled with a unique kit number assigned to the participant via IWRS.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Patient characteristics were well balanced between the two groups.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes, it is a double-blind study.
Were there any unexpected imbalances in drop-outs between groups?	No. Authors reported the number of patients and reasons for discontinuation in both treatment groups and these were balanced between groups.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. Authors measured and reported all the outcome as per study primary and secondary endpoints stated in method section.
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. This was a FAS analysis for measuring efficacy and mITT for safety outcomes, but no methods were used to account for missing data.

B.3.6 Clinical effectiveness results of the relevant studies

B.3.6.1 Summary of key efficacy outcomes

A summary of the key efficacy results from ARANOTE is presented in Table 12. ARANOTE met its primary endpoint (primary completion analysis; data cut-off [DCO]: Jun 7, 2024), showing darolutamide + ADT significantly reduced the risk of rPFS or death by 46% (HR, 0.54; 95% CI, 0.41–0.71; Table 12).[3] The rPFS benefit was consistent across all sub-groups, including age and race, baseline functioning (ECOG PS), and disease burden, including by tumour volume (high and low volume) and tumour location (with / without visceral metastases).[3] ARANOTE is the second positive

trial for darolutamide in mHSPC[89] and the second positive trial in prostate cancer for darolutamide as a doublet,[16, 137] supported by results from ARASENS[89] and ARAMIS,[16, 137] respectively. A summary of outcomes from all three trials is presented in Table 13.

At final OS analysis [redacted], there was a [redacted] for OS ([redacted]) vs placebo + ADT,[116] and clinical benefit was clear and consistently seen across all other secondary endpoints (Table 12).[3] Darolutamide + ADT delayed progression to end-stage disease mCRPC and resulted in deep and durable PSA responses,[3] similar to the ARASENS study (the pivotal trial for triplet therapy: darolutamide + ADT + docetaxel).[44] Furthermore, darolutamide + ADT demonstrated a patient-relevant HRQoL benefit, as observed in BPI-SF results.[3]

Table 12: Key efficacy outcomes reported in ARANOTE*†

	Darolutamide + ADT (n=446)		Placebo + ADT (n=223)		
	Median, months	**Events, No (%)**	**Median, months**	**Events, No.**	**HR[a] (95% CI; p value)**
Primary endpoint					
rPFS	NR	128 (28.7)	25.0	94 (42.2)	0.54 (0.41–0.71; one-sided p<0.0001)
Secondary endpoints					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to CRPC	NR	154 (34.5)	13.8	143 (64.1)	0.40 (0.32–0.51; one-sided p <0.0001)
Time to PSA progression	NR	93 (20.9)	16.8	108 (48.4)	0.31 (0.23–0.41; one-sided p <0.0001)
Time to initiation of subsequent systemic anticancer therapy	NR	68 (15.2)	NR	74 (33.2)	0.40 (0.29–0.56; one-sided p <0.0001)
Time to pain progression (BPI-SF)	NR	124 (27.8)	29.9	79 (35.4)	0.72 (0.54–0.9; one-sided p =0.0115)
PSA rates					
Detectable PSA values ≥0.2 ng/ml at baseline, N (%)[b] [95% CI]	425 (100.0)		211 (100.0)		
PSA undetectable rates (<0.2 ng/mL), n (%) [95% CI]	266 (62.6) [57.8–67.2]		39 (18.5) [13.5–24.4]		Rate difference[c]: 44.3 (37.4–51.2; one-sided p <0.0001)

*The primary endpoint rPFS and all secondary endpoints (other than OS) are from the primary completion analysis DCO Jun 7, 2024; OS and safety data presented are from the final OS analysis DCO [redacted]

†Secondary efficacy endpoints were tested for statistical significance using a hierarchical gatekeeping procedure only if the primary endpoint was statistically significant (two-sided alpha of 0.05) using the same alpha in the following order: OS, time to initiation of subsequent systemic anticancer therapy, time to CRPC, time to PSA progression, rates of PSA <2 ng/mL, and time to pain progression, as such the p values for secondary endpoints are nominal

[a]Hazard ratio and 95% CI are based on Cox regression model, stratified by visceral disease (present vs absent) and prior local therapy (yes vs no). [b]Percentages are based on participants who had a detectable PSA value at

baseline. [c]The rate difference and 95% CI were based on a Cochran-Mantel-Haenszel test comparing between the treatment arms, stratified by IWRS stratification factors: visceral metastases (present vs. absent) and prior local therapy (yes vs. no).

Abbreviations: ADT: androgen-deprivation therapy; BPI-SF: Brief Pain Inventory: Short Form; CI: confidence interval; HR: hazard ratio; mCRPC: castration-resistant prostate cancer; NA: not applicable; NR: not reached; OS: overall survival; rPFS: radiological progression-free survival PSA: prostate-specific antigen.

Source: ARANOTE Clinical Study Report September 2024, Bayer AG[4]; Saad *et al.* 2024[3]; ARANOTE Final Overall Survival Results [redacted], Bayer AG.[116]

A significant OS benefit for darolutamide has already been shown in the ARASENS study in the same patient population,[89] thus ARANOTE was specifically designed to confirm rPFS survival and was not powered for overall survival. rPFS is a well-recognised clinical endpoint and accepted surrogate endpoint for OS that allows for efficient evaluation of treatment effectiveness and enables patients to benefit from treatment sooner.[139] ARANOTE builds upon clinical evidence in mHSPC from ARASENS,[89] which resulted in a positive recommendation by NICE for use of darolutamide + ADT + docetaxel in mHSPC (TA903).[140]

The final OS analysis showed a there was [redacted], and a higher proportion of patients in the darolutamide + ADT arm vs placebo + ADT were alive at [redacted]Expert clinicians in England and Wales assert that because an OS benefit was shown for darolutamide in ARASENS in the same patient population, there is no biological rationale for darolutamide not to improve survival against ADT alone. Expert clinicians have confirmed they would be confident in prescribing darolutamide based on the collective body of supportive evidence available from ARANOTE,[3] ARASENS[89] and ARAMIS[16, 137] that shows clinically meaningful survival benefits for darolutamide in prostate cancer across all trials.[3, 16, 89, 137]

A summary of the efficacy outcomes from ARAMIS and ARASENS is presented in Table 13. In ARASENS, darolutamide + ADT + docetaxel triplet significantly reduced the risk of death by 32.5% when compared with placebo.[89] Furthermore, patients' 4-year survival rate increased to 63% for darolutamide triplet from 50% for placebo.[89] In ARAMIS, darolutamide treatment resulted in a significant 31% risk reduction for death compared with placebo in patients with nmCRPC. The survival benefit in ARAMIS for darolutamide vs placebo was shown even though over 55% of the patients in the placebo group received subsequent life-prolonging therapy.[16, 137] A real-world evidence study (DEAR) in nmCRPC showed greater clinical benefits with darolutamide

vs other ARTAs in clinical practice, with lower rates and a significant reduction in risk of disease progression to mCRPC.[125] A recent RWE study conducted in the UK in mHSPC using darolutamide + docetaxel + ADT suggested tolerability and efficacy outcomes similar to ARASENS.[141]

Table 13: Summary of primary and secondary outcomes from pivotal phase III darolutamide prostate cancer trials (ARANOTE, ARASENS and ARAMIS)

Study	ARANOTE		ARASENS		ARAMIS		ARAMIS (3-year data)	
Patient type	mHSPC				mCRPC			
	Darolutamide + ADT (n=446)	Placebo + ADT (n=223)	Darolutamide + ADT + docetaxel (n=651)	Placebo + ADT (n=655)	Darolutamide + ADT (n=955)	Placebo + ADT (n=554)	Darolutamide + ADT (n=955)	Placebo + ADT (n=554)
rPFS[a]	NR	25.0	-	-	36.8	14.8	-	-
HR[a] (95% CI; p value)	0.54 (0.41–0.71; one-sided p<0.0001)		-		0.38 (0.32–0.45; p<0.001)		-	
Metastasis-free survival[a]	-	-	-	-	40.4	18.4	-	-
HR (95% CI; p value)	-		-		0.41 (0.34–0.50; p<0.001)		-	
OS[a]	NR	NR	NE (NE–NE)	48.9 (44.4–NE)	NR	NR	% patients alive (95% CI)[a,]	
							83 (80–86)	77 (72–81)
HR (95% CI; p value)	[redacted])		0.68 (0.57–0.80; p<0.001)		0.71 (0.50–0.79; p=0.045)		0.69 (0.53–0.88; p=0.003)	
Time to CRPC[a]	NR	13.8	NE (NE–NE)	19.1 (16.5–21.8)	-	-	-	-
HR (95% CI; p value)	0.40 (0.32–0.51)		0.36 (0.30–0.42); p<0.0001		-		-	
Time to PSA progression[a]	NR	16.8	NE (NE–NE)	22 (22–28)	33.2	7.3	-	-
HR (95% CI; p value)	0.31 (0.23–0.41)		0.26 (0.21-0.31; p<0.0001		0.13 (0.11–0.16; p<0.001)		-	

Time to initiation of subsequent systemic anticancer therapy[a]	NR	NR	NE	25.3	NR	NR	% (95% CI) of patients who had not had event	
							94 (92–96)	87 (83 – 90)
HR (95% CI; p value)	0.40 (0.29–0.56)		0.39 (0.33–0.46); p<0.001		-		0.42 (0.28–0.62)	
Time to pain progression (BPI-SF) [a]	NR	29.9	NE	27.5	40.3	25.4	% (95% CI) of patients who had not had event	
							53 (47–60)	32 (22–43)
HR (95% CI; p value)	0.72 (0.54–0.9)		0.79 (0.66–0.95; p<0.001)		0.65 (0.53–0.79; p<0.001)		0.65 (0.53–0.79)	

[a]Median, months

Abbreviations: ADT: androgen-deprivation therapy; BPI-SF: Brief Pain Inventory: Short Form; CI: confidence interval; HR: hazard ratio; mCRPC: castration-resistant prostate cancer; NA: not applicable; NE, not estimable; NR: not reached; OS: overall survival; rPFS: radiological progression-free survival PSA: prostate-specific antigen.

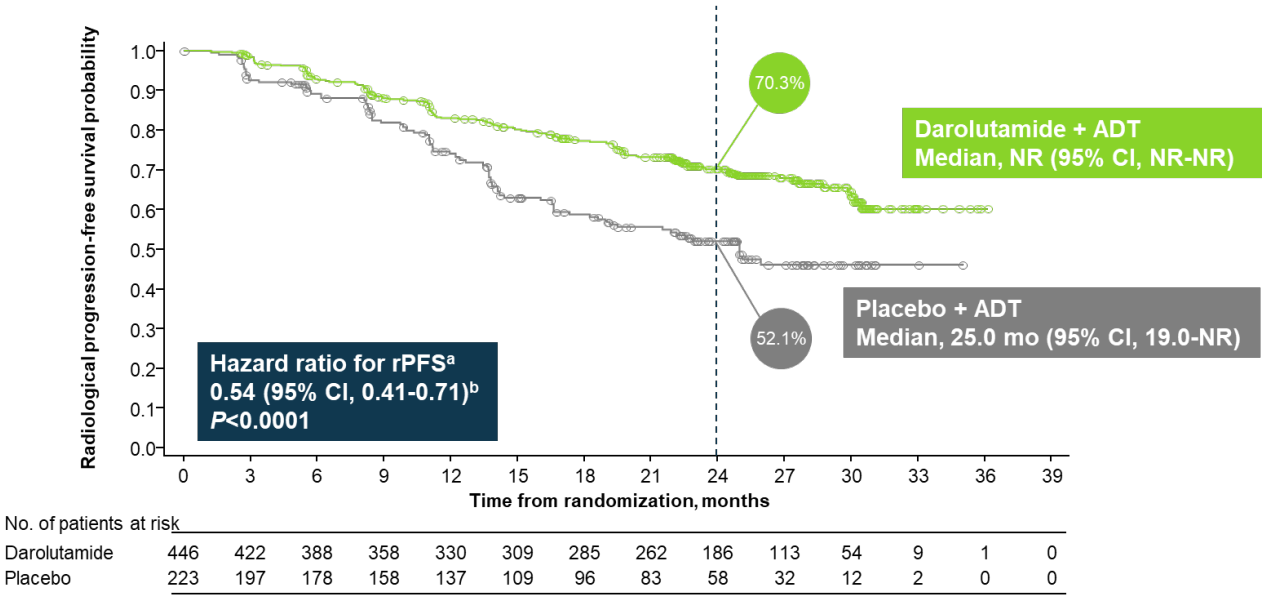
Source: ARANOTE Clinical Study Report September 2024, Bayer AG[4]; Saad *et al.* 2024[3]; Smith et al, 2022[89]; Fizazi et al, 2019[137]; Fizazi et al, 2020.[16]

B.3.6.2 Primary endpoint

As previously stated, rPFS is a well-established primary endpoint in oncology trials and acts as a surrogate for OS, allowing for a more efficient evaluation of survival benefits.[139] At the data cut-off for the primary completion analysis (DCO: June 7, 2024), the median follow-up for rPFS was 25.3 months in the darolutamide arm and 25.0 months in the placebo arm.[3]

The ARANOTE study met its primary endpoint with a statistically significant improvement and clinically meaningful benefit in rPFS for darolutamide compared to placebo arm. At database cut-off for the primary completion analysis, the darolutamide arm significantly reduced the risk of rPFS or death by 46% (HR, 0.54; 95% CI, 0.41 to 0.71; P<0.0001; Figure 3). The median rPFS was not reached in the darolutamide arm vs 25.0 months in the placebo arm.[3] At 24 months, the rPFS rate was 70.3% in the darolutamide arm vs 52.1% in the placebo arm.[3] The robustness of the rPFS analysis was confirmed by all prespecified sensitivity analyses.[4]

Figure 3: rPFS Kaplan-Meier estimates (Full analysis set)



[a]Primary analysis occurred after 222 events (darolutamide 128; placebo 94). [b]HR and 95% CI were calculated using the Cox model stratified on visceral metastases (Y/N) and prior therapy (Y/N).

Abbreviations: ADT: androgen-deprivation therapy; HR: hazard ratio; NR: not reached; rPFS: radiological progression-free survival.

Source: Saad *et al.* 2024.[3]

B.3.6.3 Secondary endpoints

B.3.6.3.1 Overall survival

At the primary completion analysis (DCO: Jun 7, 2024), a total of 163 OS events had occurred and analysis of OS showed a positive trend in favour of darolutamide compared with placebo (HR of 0.81 with 95% CI: 0.59; 1.12 and one-sided p=0.1007).[3] At the time of final OS analysis (DCO: [redacted]), a total of [redacted] OS events had occurred: [redacted] participants in the darolutamide arm and [redacted] in the placebo arm.

At final OS analysis, darolutamide reduced the risk of death by [redacted] (Figure 4). Final OS analysis results [redacted] darolutamide + ADT vs placebo + ADT ([redacted]).[116] This result [redacted] The median OS was [redacted] in either treatment arm. At 42 months, [redacted] participants in the darolutamide arm vs the placebo arm were alive.[116] OS subgroup analyses showed consistent results across all pre-planned subgroups (including age, race, and baseline PSA values, ECOG PS and Gleason scores), with HRs <1.

Participants were permitted to cross over from placebo to darolutamide at primary completion analysis. A total of [redacted] patients crossed-over from placebo to darolutamide, [4] Sensitivity analyses were conducted to allow the estimate of treatment effect as if there had been no treatment switching (rank preserving structural failure time [RPSFT) and iterative parameter estimate [IPE]). Results from both crossover adjustment methods were consistent with the final OS analyses.

[redacted]

- [redacted][116]

Figure 4: OS Kaplan-Meier estimates (Full analysis set)

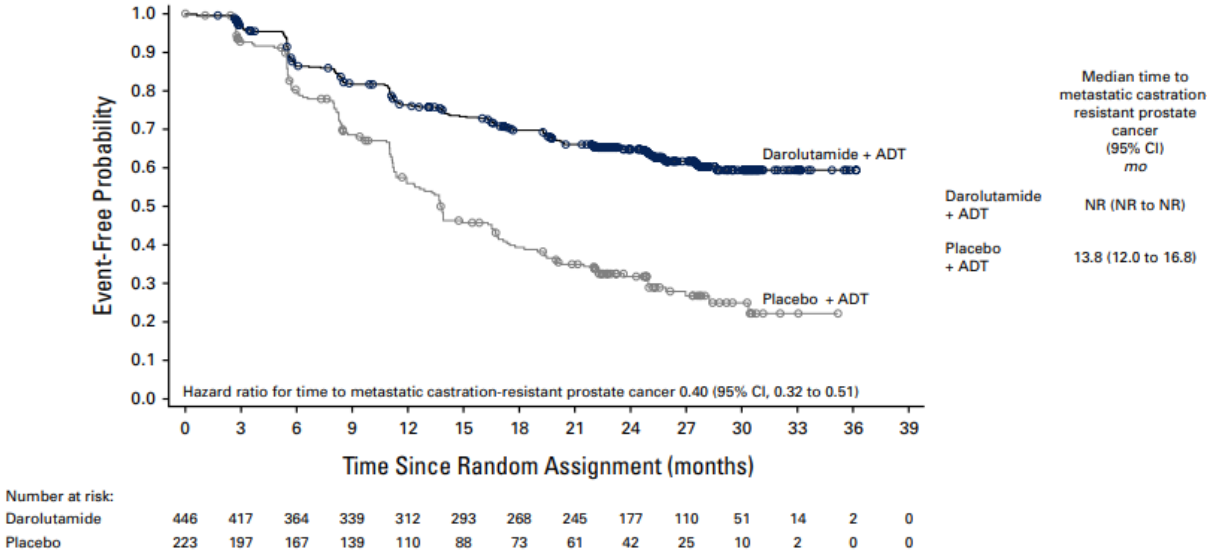
At-risk participant counts were calculated as at the start of the timepoint.

Source: ARANOTE Final Overall Survival Results [redacted], Bayer AG.[116]

B.3.6.3.2 Time to mCRPC

Darolutamide delayed time to mCRPC compared to placebo (HR, 0.40; 95% CI, 0.32–0.51), a clear benefit in favour of darolutamide, and a key patient-relevant endpoint (Figure 5).[3] The median time to mCRPC was not reached in the darolutamide arm and was 13.8 months in the placebo arm.[4] At primary completion analysis, a smaller percentage of patients in the darolutamide arm (34.5%) progressed to mCRPC than in the placebo arm (64.1%).[4] Compared to placebo, darolutamide reduced the risk of progression to mCRPC by 60%.[3] The beneficial effect of darolutamide compared with placebo on time to mCRPC was confirmed through sensitivity analysis.[4]

Figure 5: Time to mCRPC Kaplan Meier (Full analysis set)



Hazard ratios and 95% CIs were calculated using the Cox regression model stratified by the presence of visceral metastases and prior therapy.

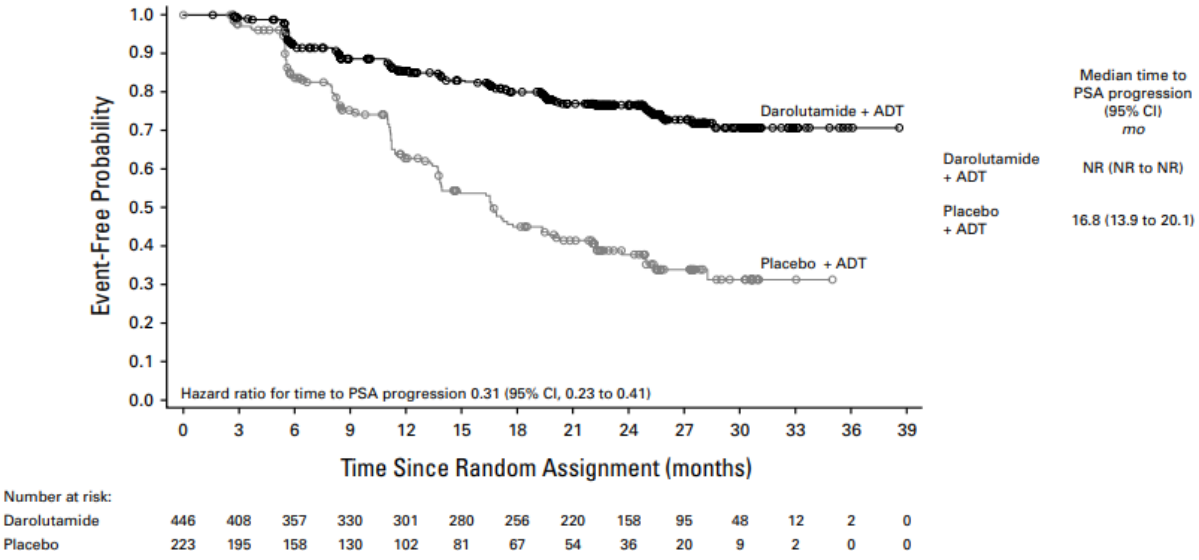
Abbreviations: ADT: androgen-deprivation therapy; NR: not reached; PSA: prostate-specific antigen.

Source: Saad *et al.* 2024.[3]

B.3.6.3.3 Time to PSA progression

Darolutamide was associated with deep and durable PSA responses (Figure 6). At primary completion analysis, darolutamide substantially prolonged the duration of time to PSA progression compared to placebo by 69% (HR, 0.31; 95% CI, 0.23–0.41]).[3] The median time to PSA progression was not reached in the darolutamide arm and was 16.8 months in the placebo arm.[4] A smaller percentage of participants in the darolutamide arm (20.9%) than in the placebo arm (48.4%) had PSA progression based on central PSA assessment.[4]

Figure 6: Time to PSA progression Kaplan Meier (Full analysis set)



Hazard ratios and 95% CIs were calculated using the Cox regression model stratified by the presence of visceral metastases and prior therapy.

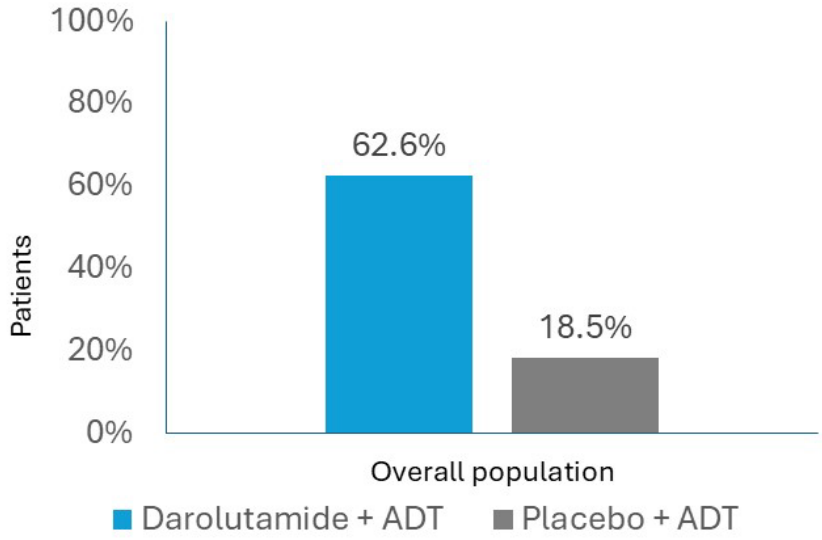
Abbreviations: ADT: androgen-deprivation therapy; NR: not reached; PSA: prostate-specific antigen.

Source: Saad *et al.* 2024.[3]

B.3.6.3.4 PSA undetectable rates (<0.2 ng/mL) at any time during treatment

A higher proportion of patients in the darolutamide arm than in the placebo arm achieved PSA <0.2 ng/ml at any time during the treatment period (62.6% vs 18.5%; Figure 7) at primary completion analysis,[3] with a rate difference of 44.3% (95% CI: 37.4–51.2; p<0.0001).[4] The PSA responses in ARANOTE support the deep and durable PSA responses with darolutamide also seen in ARASENS.[4]

Figure 7: Proportion of patients with PSA <0.2 ng/mL at any time (Full analysis set)

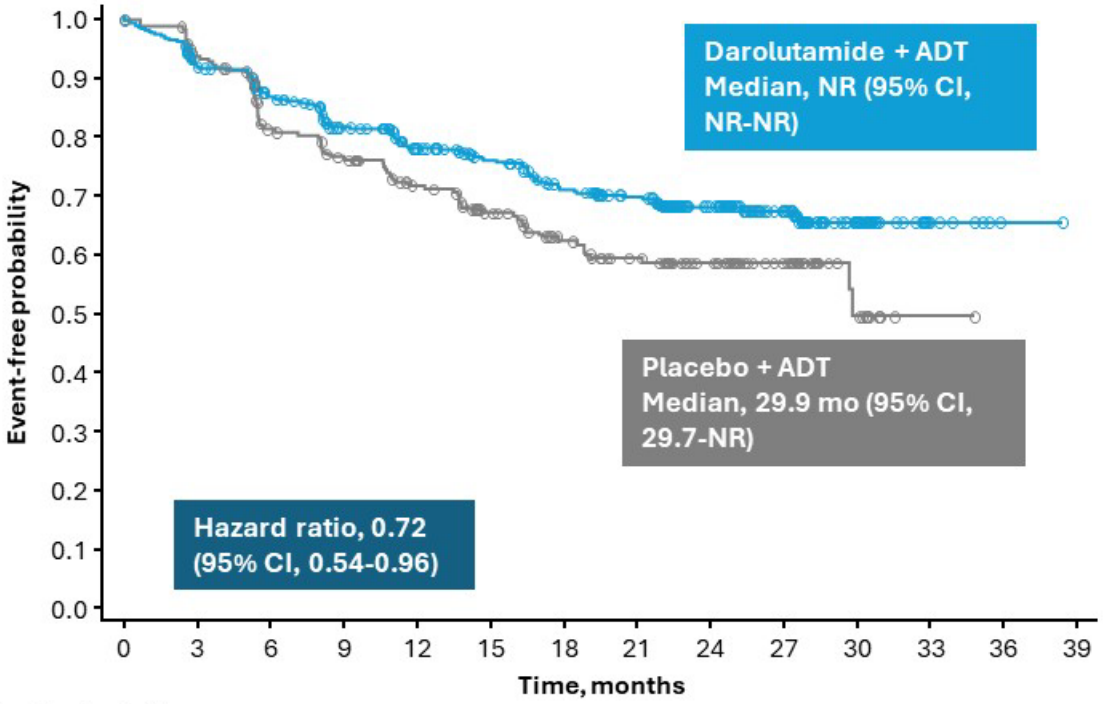


Abbreviations: ADT: androgen-deprivation therapy; PSA: prostate-specific antigen.
Source: ARANOTE Clinical Study Report September 2024, Bayer AG.[4]

B.3.6.3.5 Time to pain progression

A lower percentage of patients in the darolutamide arm vs the placebo arm had pain progression (27.8% vs 35.4%) at primary completion analysis.[4] Darolutamide delayed time to pain progression when compared with placebo (HR, 0.72; 95% CI, 0.54–0.96), a key patient-relevant endpoint, as assessed using the BPI-SF questionnaire and/or the initiation of opioid use for ≥7 consecutive days after randomisation (Figure 8).[3] The median time to pain progression was not reached in the darolutamide arm and was 29.9 months in the placebo arm.[4] At 24 months, more patients in the darolutamide than placebo arm were event-free without pain progression (68.0% vs 58.5%).[4] Sensitivity analysis results on time to pain progression were consistent with the primary completion analysis.

Figure 8: Time to pain progression Kaplan Meier (full analysis set)



No. of patients at risk

Darolutamide	446	385	349	310	278	254	225	209	150	90	36	7	1	0
Placebo	223	195	159	146	127	106	87	74	55	31	11	1	0	0

HR and 95% CI were calculated using the Cox regression model stratified by the presence of visceral metastases and prior therapy.

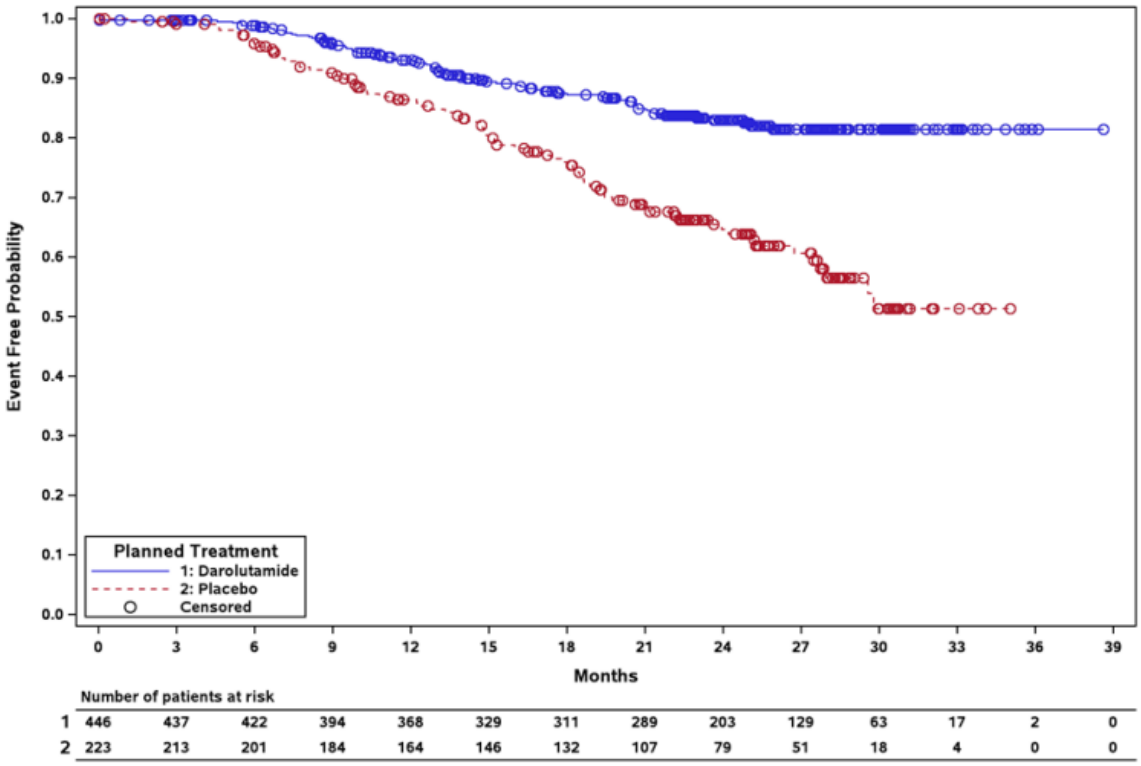
Abbreviations: ADT: androgen-deprivation therapy; HR: hazard ratio; NR: not reached.

Source: ARANOTE Clinical Study Report September 2024, Bayer AG.[4]

B.3.6.3.6 Time to initiation of subsequent systemic anticancer therapy

The time to initiation of subsequent systemic anticancer therapy was delayed in the darolutamide arm compared with the placebo arm (HR, 0.40 [95% CI, 0.29 to 0.56]; p<0.0001; Figure 9).[3] The median time to initiation of subsequent systemic anticancer therapy for prostate cancer was not reached in either of the treatment arms.

Figure 9: Time to initiation of subsequent systemic anti-cancer therapy Kaplan-Meier (full analysis set)



HR and 95% CI were calculated using the Cox regression model stratified by the presence of visceral metastases and prior therapy.

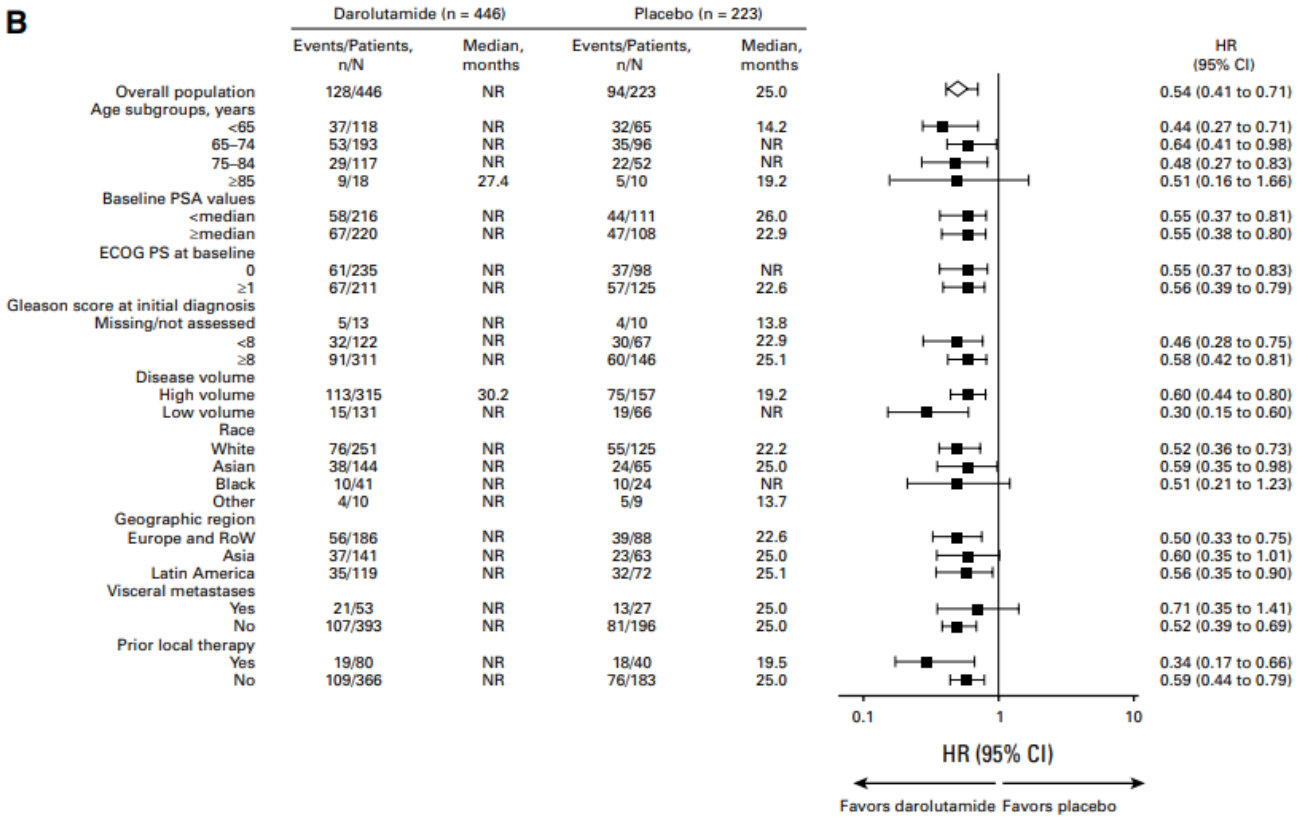
Abbreviations: ADT: androgen-deprivation therapy; HR: hazard ratio; NR: not reached.

Source: Clinical Study Report.

B.3.7 Subgroup analysis

Pre-planned subgroup analysis showed the rPFS benefit with darolutamide was consistent across all pre-specified subgroups in terms of patient demographics, including age and race, baseline functioning (ECOG PS), and by disease burden (including tumour location), and in patients with high- and low-volume mHSPC (Figure 10).[3]

Figure 10: rPFS subgroup analyses Forest plot (full analysis set)



Subgroup analyses of rPFS provide HRs and 95% CIs obtained from univariate analysis using an unstratified Cox regression model.

Abbreviations: ADT: androgen-deprivation therapy; ECOG PS: Eastern Co-operative Oncology Group performance status; HR: hazard ratio; NR: not reached; PSA: prostate-specific antigen; RoW: rest of the world; rPFS: radiological progression-free survival.

Source: Saad *et al.* 2024.[3]

B.3.8 Meta-analysis

As there is only the one RCT (ARANOTE) to support the efficacy and safety for darolutamide + ADT in mHSPC; therefore, no meta-analysis was conducted.

B.3.9 Indirect and mixed treatment comparisons

As the comparator to darolutamide + ADT for this cost-comparison submission is apalutamide + ADT, and there is no direct evidence comparing these two treatments for patients with mHSPC, a network meta-analysis (NMA) was caried out to indirectly compare the effectiveness of darolutamide + ADT and apalutamide + ADT in terms of overall survival, progression-free survival, safety and quality of life (time to deterioration of FACT-P). An NMA was possible because both treatments have been

directly compared to placebo + ADT in the ARANOTE[3] and TITAN[1] trials respectively. Full details of NMA methodology are available in Appendix D.

A comparison of the baseline characteristics of the trials included in the NMA is provided in Table 14. TITAN had a slightly higher percentage of patients with white ethnicity and ECOG status 0.[1] ARANOTE had a higher percentage of patients with visceral metastases present.[3] Overall baseline characteristics were similar.[3]

Table 14. Baseline characteristics of studies included in the NMA

Study characteristics	Treatment indicator	ARANOTE	TITAN
Number of patients	Overall	669	1,052
	Treatment	446	525
	Control	223	527
Age (yr), median	Treatment	70.0 (range: 43–93)	69 (range: 45–94)
	Control	70.0 (range: 45–91)	68 (range: 43–90)
White ethnicity, n (%)	Treatment	251 (56.3)	354 (67.4)
	Control	125 (56.1)	365 (69.3)
ECOG status 0, n (%)	Treatment	235 (52.7)	328 (62.5)
	Control	98 (43.9)	348 (66.0)
≥8 Gleason score (%)	Treatment	311 (69.7)	351 (66.9)
	Control	146 (65.5)	358 (67.9)
De-novo disease, n (%)	Treatment	317 (71.1)	411 (78.3)
	Control	168 (75.3)	441 (83.7)
High volume disease, n (%)	Treatment	315 (70.6)	325 (61.9)
	Control	157 (70.4)	335 (63.6)
Visceral metastases present, n (%)	Treatment	85 (19.1)	56 (10.67)
	Control	42 (18.8)	72 (13.66)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NMA: network meta-analysis; yr: year.
Source: Saad *et al*, 2024[3]; Chi *et al*, 2019.[1]

B.3.9.1 NMA methods

The Bayesian generalised linear model framework described in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) on evidence synthesis – TSD 2 was followed for this analysis.[142, 143] The NMA model related the data from the individual studies to basic parameters reflecting the (pooled) relative treatment effect of each intervention compared to placebo. Using these basic parameters, the relative treatment effects between each of the treatment comparisons in the network were

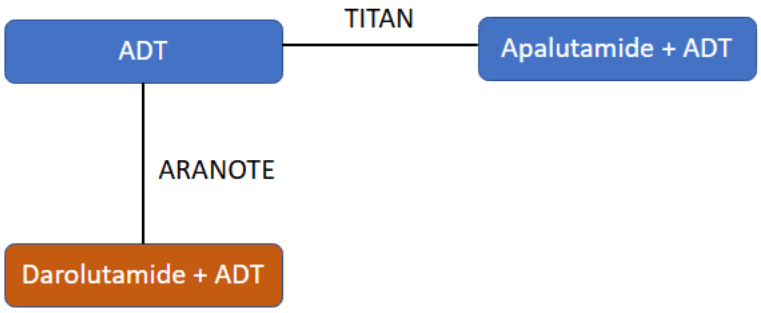
obtained and estimates of surface under the cumulative ranking (SUCRA) and mean ranks were reported.

Both fixed effects and random effects models were considered. As the evidence network was limited with only two studies included, the random effects models were unlikely to converge due to a lack of data. Therefore, predictive distributions for the heterogeneity variance were employed as informative priors (see Appendix D1.4 for full details of the methodology for the NMA). Fixed effects models were preferred a priori due to limited heterogeneity between the trials in terms of baseline characteristics (Table 14), trial design (Appendix D1.1.2) and outcome definitions (Appendix D1.1.2).

B.3.9.2 Conducted analyses

Analyses were conducted for rPFS, OS, time to deterioration in FACT-P, Grade 3-5 AEs and discontinuation due to AEs. The evidence network for all outcome measures is illustrated in Figure 11. As the ARANOTE trial was not powered to show a significant difference in OS between darolutamide + ADT and ADT alone, a surrogacy analysis was conducted to predict OS for ARANOTE. Appendix J describes the surrogacy analysis in detail. The surrogacy analyses followed the NICE decision support unit (DSU) TSD 20,[144] applying a Bayesian Bivariate random-effects meta-analysis (BRMA).[145, 146] A sensitivity analysis using the surrogate predicted OS for ARANOTE and reported OS for TITAN is presented. Input data for the NMAs are presented in Appendix D1.5. To note the OS and AE analysis, use ARANOTE data from the final OS analysis DCO [redacted], with rPFS and FACT-P data from primary completion analysis of ARANOTE DCO Jun 7, 2024.

Figure 11. Evidence network



Abbreviation: ADT: Androgen-deprivation therapy.

B.3.9.3 NMA results

B.3.9.3.1 Base case analysis for rPFS

The model assessment statistics are reported in Table 15. As the model assessment parameters show no differences between the fixed and random effects models, the fixed effects model is chosen. Rhat statistics indicated that convergence was achieved in both models (Appendix D1.6).

Table 15: Model assessment for the base case – rPFS

Model	DIC	Total residual deviance	Number of data points
Fixed effects	0.701	2.007	2
Random effects	-0.691	2.012	2

Abbreviation: DIC: Deviance Information Criteria

Base case rPFS fixed effects results comparing apalutamide + ADT with other treatments are presented in Table 16, with hazard ratios below 1 favouring apalutamide + ADT. Results show no evidence of a difference between apalutamide + ADT and darolutamide + ADT. Apalutamide + ADT has the best mean rank, followed by darolutamide + ADT while ADT monotherapy has the worst rank. Results based on a random effects model are provided in Appendix D1.7.1 and are aligned in conclusions.

Table 16: Hazard ratios for rPFS, fixed effects. Values below 1 favour apalutamide + ADT.

Treatment	HR (95% CrI)	SUCRA	Mean rank (95%CrI)
Apalutamide + ADT	Comparison	0.88	1.247 (0.998, 2.000)
Darolutamide + ADT	[redacted]	XXX	xxxxxxxxxxxxxxxx
Placebo + ADT	[redacted]	XXX	xxxxxxxxxxxxxxxx

Abbreviations: ADT: Androgen Deprivation Therapy; CrI: Credible Interval HR: Hazard Ratio; SUCRA: Surface under the cumulative ranking curve.

B.3.9.3.2 Base case analysis for OS

The model assessment statistics are reported in Table 17. The DIC favours the fixed effects model as there is limited difference (<5-point) with the random effects model. The total residual deviances indicate that both models fit the data well, with residual deviances close to the number of data points. Rhat statistics indicate that convergence was achieved in both models (Appendix D1.6). As there was an *a priori* preference for fixed effects, a fixed effect model was used in the base case.

Table 17: Model assessment for base case analysis for OS

Model	DIC	Total residual deviance	Number of data points
Fixed effects	-0.661	2.003	2
Random effects	-0669	1.999	2

Abbreviations: DIC: Deviance Information Criteria.

Results for the OS base case analysis using fixed effects are presented in Table 18 with hazard ratios below 1 favouring apalutamide + ADT. Results show no evidence of a difference between apalutamide + ADT and darolutamide + ADT. Apalutamide + ADT has the best mean rank, followed by darolutamide + ADT, although 95% CrIs are overlapping. ADT monotherapy has the worst rank. Random effects results are provided in Appendix D1.7.2 and are aligned in conclusions.

Table 18: Hazard ratios for OS base case analysis, fixed effects. Values below 1 favour apalutamide + ADT.

Treatment	HR (95%CrI)	SUCRA	Mean rank (95%CrI)
Apalutamide + ADT	Comparison	0.92	1.169 (0.998, 2.000)
Darolutamide + ADT	[redacted]	[redacted]	[redacted]
Placebo + ADT	[redacted]	[redacted]	[redacted]

Abbreviations: ADT: Androgen Deprivation Therapy; CrI: Credible Interval; HR: Hazard Ratio; SUCRA: Surface under the cumulative ranking curve.

B.3.9.3.3 Base case analysis for time to deterioration in FACT-P total score

The model assessment statistics are reported in Table 19. The DIC favours the fixed effects model as there is limited difference (<5 point) with the random effects model. The total residual deviances indicate that both models fit the data well, with residual deviances close to the number of data points. Rhat statistics indicated that convergence was achieved in both models (Appendix D1.6). There was an *a priori* preference for fixed effects, a fixed effect model was used in the base case.

Table 19: Model assessment for the base case – time to deterioration in FACT-P total score

Model	DIC	Total residual deviance	Number of data points
Fixed effects	-1.493	2.004	2
Random effects	-1.489	2.006	2

Abbreviations: DIC, Deviance Information Criteria

Base case fixed effects results comparing apalutamide + ADT with other treatments are presented in Table 20, with hazard ratios above 1 favouring other treatments against apalutamide + ADT. Results favour darolutamide + ADT against apalutamide + ADT with strong evidence of a difference. The SUCRA and mean rank for darolutamide + ADT is the best, while apalutamide + ADT has the worst rank. Random effects results are shown in Appendix D1.7.3 and are aligned in conclusions.

Table 20: Hazard ratios for base case time to deterioration in FACT-P total score, fixed effects. Values above 1 favour comparator against apalutamide + ADT.

Treatment	Hazard Ratio (95%CrI)	SUCRA	Mean rank (95%CrI)
Darolutamide + ADT	[redacted]	[redacted]	[redacted]
ADT	[redacted]	[redacted]	[redacted]
Apalutamide + ADT	Comparison	0.22	2.565 (1.997, 3.004)

Abbreviations: CrI, Credible Interval; SUCRA, Surface under the cumulative ranking curve; ADT, Androgen Deprivation Therapy

B.3.9.3.4 Base case analysis for Grade 3-5 AEs

The model assessment statistics are reported in Table 21. There is limited difference (<5 point difference) in DIC between the random and fixed effects models. The total residual deviances indicate that both models fit the data well, with residual deviances

close to the number of data points. As there was an *a priori* preference for fixed effects, a fixed effect model was used in the base case.

Table 21: Model assessment for the base case – Grade 3-5 AEs

Model	DIC	Total residual deviance	Number of data points
Fixed effects	35.98	4.010	4
Random effects	35.94	3.990	4

Abbreviations: DIC: Deviance Information Criteria.

Base case fixed effects results comparing apalutamide + ADT with other treatments are presented in Table 22, with rate ratios above 1 favouring darolutamide + ADT. A high mean rank indicates a higher risk of grade 3-5 AEs. Results favour darolutamide + ADT against apalutamide + ADT but without strong evidence of a difference. Apalutamide + ADT ranks worst amongst the treatments included, indicating higher risk of adverse events on apalutamide +ADT. Random effects results are shown in Appendix D1.7.4 and are aligned in conclusions.

Table 22: Rate ratios for grade 3-5 AEs, fixed effects. Values below 1 favour comparator against apalutamide + ADT

Treatment	Rate Ratio (95%CrI)	SUCRA	Mean rank (95%CrI)
ADT	[redacted]	[redacted]	[redacted]
Darolutamide + ADT	[redacted]	[redacted]	[redacted]
Apalutamide + ADT	Comparison	0.08	2.842 (1.998, 3.002)

Abbreviations: ADT: Androgen Deprivation Therapy; AEs: Adverse events; CrI: Credible Interval; SUCRA: Surface under the cumulative ranking curve

B.3.9.3.5 Base case analysis for discontinuation due to AEs

The model assessment statistics are reported in Table 23. There is limited difference in DIC between the random and fixed effects models. The total residual deviances indicate that both models fit the data well, with residual deviances close to the number of data points. As there was an *a priori* preference for fixed effects, a fixed effect model was used in the base case.

Table 23: Model assessment for the base case – Discontinuation due to AEs

Model	DIC	Total residual deviance	Number of data points
Fixed effects	29.28	4.040	4
Random effects	29.25	4.026	4

Abbreviations: DIC: Deviance Information Criteria

Base case fixed effects results comparing apalutamide + ADT with other treatments are presented in Table 24, with rate ratios above 1 favouring darolutamide + ADT. A high mean rank indicates a higher risk of discontinuation due to AEs. There is evidence of a strong difference favouring darolutamide + ADT against apalutamide + ADT. Darolutamide + ADT ranks best, while apalutamide + ADT ranks worst amongst the treatments included. Base case random effects results are shown in Appendix D1.7.5 and are aligned in conclusion.

Table 24: Rate ratios for discontinuation due to AEs, fixed effects. Values below 1 favour comparator against apalutamide + ADT

Treatment	Rate Ratio (95%CrI)	SUCRA	Mean rank (95%CrI)
Darolutamide + ADT	[redacted]	[redacted]	[redacted]
ADT	[redacted]	[redacted]	[redacted]
Apalutamide + ADT	Comparison	0.00	2.998 (2.998, 3.002)

Abbreviations: ADT: Androgen Deprivation Therapy; AEs: Adverse events; CrI: Credible Interval; SUCRA: Surface under the cumulative ranking curve

B.3.9.4 Uncertainties in the indirect and mixed treatment comparisons

The main limitations of the indirect treatment comparisons are the sparse network of evidence and the fact that ARANOTE was not powered to show a significant difference in OS between darolutamide + ADT and ADT alone. As mentioned in Section B.3.9.2, surrogate OS was predicted to address this uncertainty. Clinicians were consulted regarding the use of the predicted surrogate OS. They understood the rationale behind the surrogacy analysis but emphasised that the surrogate data should be considered supplementary. This is because darolutamide has already shown a survival advantage in two earlier prostate cancer trials, ARASENS[89] and ARAMIS,[137] of which ARASENS included a patient population similar to the ARANOTE trial.[3, 89]

Most clinicians expressed confidence in prescribing darolutamide + ADT based on the interim OS data from ARANOTE, the OS data which was available at the time of validation, as darolutamide had demonstrated both efficacy and safety in previous trials. They indicated that the final OS data would not change their perspective. Furthermore, they noted the significant rPFS demonstrated in the trial, recognising from experience that a strong rPFS hazard ratio often correlates with OS benefit. Additionally, given darolutamide's positive survival outcomes in other trials, clinicians

felt confident in its life-extending potential. The survival benefit seen in prior trials reassured them more than relying solely on the surrogate data.[80] To address the uncertainty regarding ARANOTE OS data, a sensitivity analysis was conducted where the predicted surrogate OS for ARANOTE is used instead.

B.3.9.4.1 Sensitivity analysis for OS (using surrogate OS for ARANOTE and reported OS for TITAN)

The model assessment statistics are reported in Table 25. The DIC favours the fixed effects model however there is limited difference with the random effects model. The total residual deviances indicate that both models fit the data well, with residual deviances close to the number of data points. Rhat statistics indicated that convergence was achieved in both models (Appendix D1.6).[147] As there was an *a priori* preference for fixed effects, a fixed effect model was used in the base case.

Table 25: Model assessment for the sensitivity analysis – OS

Model	DIC	Total residual deviance	Number of data points
Fixed effects	0.7374	1.999	2
Random effects	0.7365	1.999	2

Abbreviation: DIC: Deviance Information Criteria.

Base case fixed effects results comparing apalutamide + ADT with other treatments in the network are presented in Table 26 with hazard ratios below 1 favouring apalutamide + ADT. Results show no evidence of a difference between apalutamide + ADT and darolutamide + ADT. The SUCRA and mean rank are very similar for apalutamide + ADT and darolutamide + ADT, with almost overlapping 95% CrI on the latter, while ADT monotherapy has the worst rank. Random effects results are shown in Appendix D1.7.6 and are aligned in conclusions.

Table 26: Hazard ratios for sensitivity analysis OS, fixed effects. Values below 1 favour apalutamide + ADT.

Treatment	HR (95% CrI)	SUCRA	Mean rank (95%CrI)
Apalutamide + ADT	Comparison	0.74	1.516 (1.000, 2.000)
Darolutamide + ADT	[redacted]	[redacted]	[redacted]
Placebo + ADT	[redacted]	[redacted]	[redacted]

Abbreviations: ADT: Androgen Deprivation Therapy; CrI: Credible Interval; HR: Hazard Ratio; SUCRA: Surface under the cumulative ranking curve.

B.3.10 Adverse reactions

Summary

- ARANOTE safety outcomes reconfirm the established, favourable tolerability of darolutamide previously shown in the ARAMIS and ARASENS trials.[3, 6, 89]
- ARANOTE is the first and only study of an ARTA in prostate cancer to show placebo-like safety outcomes.[3, 116]
    - Rates of the most common AEs occurring in ≥5% of patients with darolutamide + ADT in the double-blind (DB) plus open-label extension (OLE) period were low, mostly Grade 1 or Grade 2 events, and similar to placebo + ADT, confirming its favourable tolerability.
    - Similar and low rates of TEAEs (Any, Serious and Grade 3 or 4) for darolutamide + ADT vs placebo + ADT were also found in the DB period, and for darolutamide + ADT through the OLE period.
- ARANOTE showed low incidences of AEs associated with other ARTAs that could impact patient ADL including CNS events (e.g., fatigue and mental impairment), cardiovascular events, and rash.[116]
    - Hypertension is a frequently reported AE with ARTA therapy in mHSPC; however, in ARANOTE, similar and low proportions of patients with hypertension were reported for darolutamide (DB and DB + OLE periods: [redacted] and [redacted]) and placebo ([redacted]), with a lower exposure adjusted incident rate (EAIR) for darolutamide vs placebo ([redacted]).[116]
- Treatment emergent EAIRs suggest similar rates of AEs that may impact patients' activities of daily living (such as CNS event, cardiovascular events, diabetes/hyperglycaemia, and rash) for darolutamide + ADT and placebo + ADT.[116]
- ARANOTE is the only ARTA study across pivotal prostate cancer clinical trials to show lower discontinuation rates due to AEs in the treatment arm vs the placebo arm ([redacted]) [116] and means patients stay on beneficial treatment for longer.[1-3, 6, 16, 69, 89, 110, 148-150]

- There was no increased safety signal for darolutamide in ARANOTE in AEs considered to be important safety considerations with apalutamide, including rash, and fatigue, and hypothyroidism.
    - Darolutamide-treated patients had a [redacted] lower rate of fatigue vs placebo ([redacted] across both DB and OLE periods.[116]
    - During the DB and OLE periods, a low percentage of darolutamide vs placebo-treated patients had rash ([redacted]), with an EAIR that was low and the same for both arms ([redacted]) during the DB period.[116]
- Seizure has been reported in patients treated with apalutamide, but no patients had a TEAE of seizure in ARANOTE, including the participant with a history of epilepsy.[4]
- Results from an indirect treatment comparison an indirect treatment comparison comparing published results from TITAN[1] with ARANOTE[3] data found:
    - Patients treated with apalutamide + ADT are at higher risk of Grade 3–5 AEs compared with patients treated with darolutamide + ADT or ADT monotherapy.
    - A higher risk of treatment discontinuation due to an AE for patients treated with apalutamide + ADT compared with darolutamide + ADT or ADT monotherapy

Safety evidence for darolutamide + ADT in mHSPC is provided by the phase III ARANOTE pivotal study from DCO: [redacted] (final OS analysis).[116] Safety data showed darolutamide + ADT is well tolerated and has a favourable safety profile, consistent with the established safety profile observed at final completion analysis,[3, 4] with no new safety findings.[116]

A summary of treatment emergent adverse events (TEAEs) is presented in Table 27. The overall treatment-emergent adverse event (TEAE) incidence was comparable across the darolutamide DB period, placebo DB period, and darolutamide DB and OLE

period ([redacted] respectively), with low and similar incidences of AEs. In ARANOTE, most AEs were Grade 1 or Grade 2, and similar rates of Grade 3, 4, or 5 AEs, and serious AEs were observed for darolutamide during the DB and OLE period and for placebo (DB period). The overall TEAE incidence ([redacted]) was lower for participants who crossed over from placebo to darolutamide. However, this is likely due to the shorter timeframe after crossover versus before crossover.[116] Fewer patients in the darolutamide arm than placebo arm discontinued treatment due to adverse events in the DB period ([redacted], with the same low number of discontinuations of [redacted] for patients on darolutamide for the study duration.[116]

The similar rates of TEAEs across treatment arms and lower rate of discontinuations in the darolutamide arm in ARANOTE reconfirm the established tolerability of darolutamide seen in ARAMIS and ARASENS.[3, 6, 89] ARANOTE is the only ARTA-based study in prostate cancer to show lower discontinuation rates due to AEs in the treatment vs the placebo arm,[3, 116] and means patients are more likely to stay on beneficial treatment for longer.

Table 27: Summary of TEAEs (safety analysis set)

AE, n (%)	Darolutamide + ADT (DB) (N=446)	Darolutamide + ADT (DB + OL) N=446	Placebo + ADT (N=220[a])	Placebo-darolutamide (crossover period; N=59)
Any AE	[redacted]	[redacted]	[redacted]	[redacted]
Serious AE	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3 or 4 AE	[redacted]	[redacted]	[redacted]	[redacted]
Grade 5 AE	[redacted]	[redacted]	[redacted]	[redacted]
AE leading to permanent discontinuation of study drug	[redacted]	[redacted]	[redacted]	[redacted]
AE leading to dose modification	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADT: androgen deprivation therapy; AE: adverse event; DB: double-blind; OL: open-label; SAS: safety analysis set; TEAE: treatment-emergent adverse event.

Source: ARANOTE Final Overall Survival Results [redacted], Bayer AG.[116]

B.3.10.1 Adverse events

The rates of most common TEAEs with darolutamide were low and similar to placebo during the DB and the OLE period, confirming darolutamide's favourable tolerability (Table 28). The most common (≥10%) Any Grade TEAEs in the darolutamide (DB period and DB plus OLE period) vs placebo arm (DB period) were anaemia ([redacted]), arthralgia ([redacted]), urinary tract infection ([redacted] and back pain ([redacted]). The most common (≥2%) Grade 3 or 4 TEAEs for darolutamide (DB period and DB plus OLE period) vs placebo (DB period) were hypertension ([redacted]), anaemia ([redacted] increased aspartate aminotransferase (AST) [redacted] increased alanine aminotransferase (ALT) ([redacted]), and bone pain ([redacted]).

Table 28: TEAEs in ≥5% of participants (safety analysis set)

	Darolutamide + ADT (DB) N=446		Darolutamide + ADT (DB & OL) N=446		Placebo + ADT (DB) N=220		Placebo-Daro (crossover period) N=59	
n (%)	**Any grade**	**Grade 3 or 4**	**Any grade**	**Grade 3 or 4**	**Any grade**	**Grade 3 or 4**	**Any grade**	**Grade 3 or 4**
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increased aspartate aminotransferase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hot flush	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increase alanine aminotransferase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increased weight	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Darolutamide + ADT (DB) N=446		Darolutamide + ADT (DB & OL) N=446		Placebo + ADT (DB) N=220		Placebo-Daro (crossover period) N=59	
n (%)	**Any grade**	**Grade 3 or 4**	**Any grade**	**Grade 3 or 4**	**Any grade**	**Grade 3 or 4**	**Any grade**	**Grade 3 or 4**
Increased alkaline phosphatase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increased creatinine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADT: androgen-deprivation therapy; COVID-19: coronavirus disease 2019.
Source: ARANOTE Final Overall Survival Results [redacted], Bayer AG.[116]

B.3.10.2 TEAEs of special interest

TEAEs of special interest commonly associated with ARTAs occurred at low and similar rates for darolutamide vs placebo (Table 29).[3] Darolutamide showed a low incidence of AEs associated with other ARTAs that impact a patient's activities of daily living, such as fatigue, rash, CNS-related AEs, falls, fractures, and hot flushes.[3] Notably, the darolutamide arm had a [redacted] lower rate of fatigue (vs placebo ([redacted]) both during the DB and OLE period. ARANOTE is the first study of an ARTA that shows a lower rate of fatigue in the treatment group compared with placebo.[116] ARANOTE had broad eligibility criteria and patients with a history of seizures were eligible for study inclusion. One patient in the darolutamide arm with a history of seizure was included in the study. No participants had a TEAE of seizure during the study, including the participant with a history of epilepsy. There were no reports of hypothyroidism as a TEAE in ARANOTE.[4]

Table 29: TEAEs of special interest (safety analysis set)

AEs commonly associated with ARTAs (n, %)	Darolutamide + ADT (DB) N=446	Darolutamide + ADT (DB & OL) N=446	Placebo + ADT (DB) N=220)	Placebo-Darolutamide (crossover period) N=59
Hypertension[a]	[redacted]	[redacted]	[redacted]	[redacted]
Vasodilatation and flushing	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes mellitus and hyperglycaemia	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac arrhythmias[a]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Rash[b]	[redacted]	[redacted]	[redacted]	[redacted]
Bone fracture[c]	[redacted]	[redacted]	[redacted]	[redacted]
Coronary artery disorders[a]	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Decreased weight	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]
Mental impairment disorder[a]	[redacted]	[redacted]	[redacted]	[redacted]
Falls, including accident	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure[a]	[redacted]	[redacted]	[redacted]	[redacted]
Depressed mood disorder[a]	[redacted]	[redacted]	[redacted]	[redacted]
Cerebral ischaemia	[redacted]	[redacted]	[redacted]	[redacted]

[a]This category is a MedDRA High-Level Group Term. [b]This category combines the following MedDRA terms: rash, maculopapular rash, papular rash, pustular rash, and dermatitis. [c]Excluding pathologic fractures. This category combines the following MedDRA terms: any fractures and dislocations, limb fractures and dislocations, pelvic fractures and dislocations, spinal fractures and dislocations, and thoracic cage fractures and dislocations.

Abbreviations: ADT: androgen-deprivation therapy; ARTA: androgen-receptor targeted agent; MedDRA: Medical Dictionary for Regulatory Activities.

Source: ARANOTE Final Overall Survival Results [redacted], Bayer AG.[116]

B.3.10.3 TEAEs exposure-adjusted incidence rates

When adjusted for treatment exposure, the rates of AEs commonly associated with ARTAs, which can impact patient's daily living, was reported to be similar across treatment arms (Table 30).[3] Notably the rate of rash was low and the same for both darolutamide and placebo (2.4). Hypertension is one of the most frequently reported AEs associated with ARTA use; however, exposure-adjusted incidence rate (EAIR) data from ARANOTE suggest a lower incidence for hypertension for darolutamide when compared with placebo ([redacted] IRR [redacted]).

Table 30: TEAE exposure-adjusted incidence rates

Adverse Events Commonly Associated With ARTAs	Darolutamide + ADT (DB) N=446	Placebo + ADT (DB) N=220	Darolutamide vs placebo (DB)
	EAIR[b]/100 PY	EAIR[b]/100 PY	Incidence Risk Ratio (IRR) for EAIR
Hypertension[a]	[redacted]	[redacted]	[redacted]
Vasodilatation and flushing	[redacted]	[redacted]	[redacted]
Diabetes mellitus and hyperglycemia	[redacted]	[redacted]	[redacted]
Cardiac arrhythmias[a]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Rash[b]	[redacted]	[redacted]	[redacted]
Bone fracture[c]	[redacted]	[redacted]	[redacted]
Coronary artery disorders[a]	[redacted]	[redacted]	[redacted]
Decreased weight	[redacted]	[redacted]	[redacted]
Mental-impairment disorder[a]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]
Falls, including accident	[redacted]	[redacted]	[redacted]
Heart failure[a]	[redacted]	[redacted]	[redacted]
Depressed-mood disorder[a]	[redacted]	[redacted]	[redacted]
Cerebral ischemia	[redacted]	[redacted]	[redacted]

[a]This category is a MedDRA High-Level Group Term. [b]This category combines the following MedDRA terms: rash, maculopapular rash, papular rash, pustular rash, and dermatitis. [c]Excluding pathologic fractures. This category combines the following MedDRA terms: any fractures and dislocations, limb fractures and dislocations, pelvic fractures and dislocations, spinal fractures and dislocations, and thoracic cage fractures and dislocations.

Abbreviations: ADT: androgen-deprivation therapy; ARTA: androgen-receptor targeted agent; EAIR: exposure-adjusted incidence rate; MedDRA: Medical Dictionary for Regulatory Activities; PY: patient years.

Source: ARANOTE Final Overall Survival Results [redacted], Bayer AG.[116]

Comparative safety summary

For the purposes of this appraisal, darolutamide is compared with apalutamide. Although darolutamide and apalutamide are from the same drug class, with the same mode of action and method of administration, darolutamide has a distinct chemical structure that differentiates it from apalutamide, resulting in reduced BBB penetration and low central nervous system side effects.[45] Fatigue frequently occurs with ARTA treatment and is a key concern among clinicians practicing in England and Wales given that it significantly impacts patient care and outcomes. In the apalutamide TITAN study, the key comparative evidence in this appraisal, fatigue was found in 19.7% vs 16.7% of apalutamide vs placebo-treated patients.[45] In contrast, in ARANOTE, levels of fatigue were 30% lower in the darolutamide than placebo arm ([redacted][116] Data also suggest darolutamide-treated patients are less likely to be at risk of treatment-related seizures than with apalutamide. Patients with a medical history of seizures were excluded from TITAN, as apalutamide use was associated with an increased risk of seizures in SPARTAN[45, 110]; despite this precaution, TITAN reported Grade ≥3 seizure in 0.2% of apalutamide-treated patients.[1] In ARANOTE, patients were not excluded from study participation on the basis of a prior history of seizures, yet there were no TEAEs of seizure. Apalutamide is thought to induce seizures due to its inhibition of GABA-A receptors,[45] whilst darolutamide has a low binding affinity for GABA-A receptors.[15, 20, 22]

ARANOTE data also showed lower incidences of adverse events that impact ADL when compared with TITAN data. Hypertension is one of the most commonly-reported AEs with ARTA therapies, and was found in 17.7% vs 15.6% (All Grades) of apalutamide vs placebo-treated patients in TITAN.[1] In comparison, EAIRs for hypertension in ARANOTE suggest incidences are lower for darolutamide than placebo ([redacted]).[116]

Dermatologic toxicities are a significant concern for patients undergoing treatment with apalutamide, and clinicians in England and Wales report they have a profound effect on patient QoL, as well as impacting HRCU.[45, 119] In TITAN, a notable 27.1% vs 8.5% of apalutamide vs placebo-treated patients experienced rash of Any Grade, and 6.3%

vs 0.6% had a Grade ≥3 rash.[1] In contrast, darolutamide showed no increased signal for rash in ARANOTE, with an EAIR of [redacted] for both darolutamide and placebo.[116]

There is also a key need for a prostate cancer agent with improved treatment discontinuation rates due to AEs. ARANOTE is the only ARTA study across prostate cancer, including TITAN, to show lower discontinuation rates due to AEs in the treatment vs placebo arm ([redacted]).[1-3, 6, 16, 69, 89, 110, 148-150] Discontinuation rates due to AEs for apalutamide vs placebo were 8.0% and 5.3% in TITAN.[1] Results from ARANOTE suggest that patients receiving darolutamide will stay on beneficial treatment for longer.[116]

The comparative safety profile between apalutamide and darolutamide is an important evidence base to consider for this appraisal, as many patients with mHSPC are unable to receive optimal treatment intensification therapy due to treatment toxicity concerns with currently available agents. There is a significant key unmet need in the mHSPC space for an ARTA with an improved tolerability profile.

B.3.11 Conclusions about comparable health benefits and safety

B.3.11.1 Conclusions from ARANOTE efficacy and safety data

The pivotal phase III trial ARANOTE[3] is the key RCT providing clinical evidence for darolutamide + ADT in patients with mHSPC. ARANOTE is a global, randomised, double-blind, placebo-controlled, phase III trial conducted in participants with mHSPC (n=669) to determine if darolutamide (600 mg twice daily) + ADT (n=446) is superior to matched placebo + ADT (n=223).[3] ARANOTE is the second positive trial for darolutamide in mHSPC[89] and the second positive trial in prostate cancer for darolutamide as a doublet,[16, 137] and supported by results from ARASENS[89] and ARAMIS,[16, 137] respectively. ARANOTE had a broad eligibility criteria, enrolling a diverse population representative of real-world patients requiring treatment in England and Wales, as confirmed by expert clinicians.[3, 80] ARANOTE met its primary endpoint, showing darolutamide + ADT significantly reduced the risk of rPFS death by 46% (HR, 0.54; 95% CI, 0.41–0.71; p<0.001), with a consistent benefit across all pre-planned subgroups.[3] These results were consistent with TITAN where apalutamide + ADT vs

placebo + ADT reduced the risk of rPFS or death by 52% (HR, 0.48; p<0.001) and increased OS by 33% (HR, 0.67; p=0.005).[1]

In ARANOTE, primary completion analysis data were suggestive of OS benefit with darolutamide + ADT[3] and this [redacted]. Results were consistent when adjusted for treatment cross-over and across all pre-specified subgroups.[116] OS data are also supported by a clear and consistent clinical benefit being observed across all other clinically meaningful and patient-relevant secondary endpoints in ARANOTE, as well as the comprehensive body of evidence from ARASENS and ARAMIS.[3, 16, 89, 137] Expert clinicians have confirmed they are confident in prescribing darolutamide based on supporting efficacy evidence across all three trials, noting that there is no biological rationale for darolutamide to improve OS in ARASENS and ARAMIS, but not in ARANOTE.[80, 82]

For patients with mHSPC, treatment-related morbidity is prevalent, enduring and essential to care decisions.[93, 94, 115] Treatment tolerability and risk of DDIs remains a key unmet need with current therapy options for mHSPC, given that it drives persistent use of sub-optimal therapy in many patients and a lack of treatment intensification, which is associated with poorer outcomes in mHSPC.[11, 23, 24, 45, 80, 82, 98, 115] The ARANOTE study is the first and only study of an ARTA to show placebo-like safety outcomes,[1-3, 45] Safety outcomes obtained in ARANOTE reconfirm the established, favourable tolerability of darolutamide previously shown in the ARAMIS and ARASENS trials.[3, 6, 89] As well as darolutamide having a safety profile similar to placebo, ARANOTE showed low incidences of AEs associated with other ARTAs that could impact patient ADL and lead to pool QoL, reduced adherence and treatment discontinuation, including cardiovascular toxicities. Of particular significance is the low incidence of fatigue and rash, and no patients reported a TEAE of hypothyroidism, which are prevalent with apalutamide use, as well as cognitive dysfunction seen with enzalutamide.[3] Darolutamide-treated patients had a [redacted] lower rate of fatigue vs placebo ([redacted]) in ARANOTE.[116]

The improved safety profile of darolutamide is attributed to its distinct chemical structure where its higher polarity and increased flexibility are associated with low BBB

penetration.[20, 21, 151] This could potentially be a factor in the lack of association between darolutamide and CNS side effects.[15, 17-19, 152] Grade 3 (serious) seizures have been found in TITAN[1] and ARCHES[2] pivotal trials for apalutamide and enzalutamide, despite patients with a prior history of seizure being excluded from these trials. The reimbursement of darolutamide + ADT by NICE will allow treatment intensification in this small but significant patient population.[80]

Furthermore, and crucially, ARANOTE is the only ARTA study across pivotal prostate cancer clinical trials to show lower discontinuation rates due to AEs in the treatment arm vs the placebo arm ([redacted]).[1-3, 6, 16, 62, 64, 69, 89, 110, 148-150] Fewer patient discontinuations with darolutamide + ADT means patients can stay on beneficial treatment for longer, which is anticipated to improve patient outcomes.[116]

Overall, clinicians in England and Wales confirm darolutamide's differentiated tolerability and low potential for DDI's (see Section B.1.3.2), may simplify treatment management and allow treatment intensification in patients with comorbidities and risks of DDIs that make them ineligible for currently available treatments.[80] APCCC 2024 consensus opinion confirms darolutamide as a better tolerated treatment option than apalutamide or enzalutamide in patients with advanced cancer, with pre-existing comorbidities, and for older patients.[111]

B.3.11.2 Conclusions from Network-Meta Analysis

As the comparator to darolutamide + ADT for this cost-comparison submission is apalutamide + ADT, and there is no direct evidence comparing these two treatments for patients with mHSPC, a network meta-analysis (NMA) was caried out to indirectly compare the effectiveness of darolutamide + ADT and apalutamide + ADT. The NMA compared rPFS, OS, time to deterioration in FACT-P, Grade 3-5 AEs and discontinuation due to AEs for darolutamide + ADT with apalutamide + ADT.

No evidence of a difference between darolutamide + ADT and apalutamide + ADT was found in terms of HR, with wide 95% CrIs. The analysis is limited by a sparse evidence network, but despite this, the analyses have indicated no difference in rPFS or OS between darolutamide + ADT and apalutamide + ADT.

The NMA was also conducted on the PRO based outcomes of time to deterioration in FACT-P score. There was strong evidence indicating that the time to deterioration in FACT-P was longer for darolutamide + ADT than on apalutamide + ADT (HR = [redacted]), suggesting improved HRQoL for darolutamide + ADT compared to apalutamide + ADT.

In addition, the NMA also analysed adverse event data with results supporting the anticipated beneficial AE profile for darolutamide when compared with apalutamide. Base case fixed effects results suggest the risk of Grade 3–5 AEs in patients treated with apalutamide + ADT is greater than darolutamide + ADT, but without strong evidence of a difference. Base case fixed effects analysis also indicated a statistically significantly higher risk of treatment discontinuation due to an AE for patients treated with apalutamide + ADT vs darolutamide + ADT or ADT monotherapy.

The results of the efficacy and safety NMA were discussed with UK clinicians at a UK advisory board meeting.[82] Both efficacy and safety results were aligned with their expectations and observations in real world clinical practice. Similar survival between the treatments, as found in the ITC was expected as both drugs are of the same class. The key difference between apalutamide and darolutamide is the beneficial safety profile of darolutamide, confirmed by the ITC, and clinicians stated this should be considered in NICE decision making.[82]

B.3.12 Ongoing studies

Other than ARANOTE, there no ongoing trials assessing the efficacy of darolutamide + ADT as an option for treating adult men with mHSPC.

B.4 Cost-comparison analysis

Summary

- As per the final scope, a cost-comparison analysis has been conducted, assuming equal efficacy and safety for darolutamide + ADT and apalutamide + ADT.
- The cost-comparison analysis shows that darolutamide + ADT generates cost savings of [redacted] at the PAS price, compared with apalutamide + ADT over the model time horizon.
- This is primarily due to lower acquisition costs for darolutamide + ADT compared with apalutamide + ADT (when the PAS price is applied).
- At the PAS price, the results remained cost-saving across all scenarios.
- Darolutamide + ADT offers several advantages over apalutamide + ADT which are conservatively not reflected within this economic analysis, including a better safety profile with fewer CNS-related adverse events, improved healthcare resource utilisation by simplifying patient management, and no additional monitoring requirements like thyroid function tests.
- While consideration of the impact of darolutamide + ADT on patient's HRQoL is out of scope for the cost-comparison analysis, it should be noted there is evidence that darolutamide + ADT demonstrates better patient-reported outcomes than apalutamide + ADT, with a longer time to deterioration in the FACT-P score.

In line with the NICE Methods Guide, a cost-comparison case can be made if a health technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication.[153] As per the decision problem in Section B.1.1 and in line with the final scope for this appraisal,[154] the comparator for this appraisal is apalutamide + ADT, which was recommended by NICE for use by the NHS in October 2021 (TA740).[84]

In Section B.3.9, the NMA results demonstrated that there is no evidence of a difference in efficacy between darolutamide + ADT and apalutamide + ADT. This was further supported by UK clinicians during both advisory board meetings, where they stated that darolutamide and apalutamide are clinically similar and recommended both as first-line treatment options for patients with mHSPC.[80 82]

Darolutamide was approved by NICE in November 2020 for use in combination with ADT to treat hormone-relapsed non-metastatic prostate cancer (nmCRPC) [TA660].[155] In June 2023, it was further approved for use with ADT and docetaxel in the treatment of hormone-sensitive metastatic prostate cancer (mHSPC) [TA903].[140] As of now, the list price of darolutamide, as listed in the BNF, is £4,040 for a pack of 112 tablets (300 mg).[156] Additionally, a simple discount PAS price of [redacted], representing a [redacted]% discount on the list price, is in place.

The list price of apalutamide is £2,735 for 112 tablets (300 mg) based on BNF.[157]

Inputs specific to the cost-comparison analysis are presented in the following sections of this dossier.

B.4.1 Changes in service provision and management

As noted in Section B.4, darolutamide was first approved by NICE in 2020 for use with ADT and later in 2023 for use with ADT and docetaxel for prostate cancer patients.[140, 155] Therefore, no additional changes to service provision or management are anticipated.

Darolutamide and the comparator, apalutamide, are both oral medications, therefore there are no differences expected in the resources needed to administer each drug.

However, in terms of drug monitoring and resource utilisation, UK clinicians highlighted several resource use benefits associated with darolutamide over apalutamide during the HEOR advisory board meeting held in February 2025.[82] They noted that when patients initiate treatment with apalutamide they require changes to concomitant medications due to DDIs, the process often involves the engagement of multiple healthcare providers, including general practitioners, hospital pharmacists, and

consultant oncologists, which can be both time-consuming and resource intensive.[82] Additionally, the clinicians highlighted that patients receiving apalutamide require thyroid function tests as part of their treatment monitoring, adding another layer of testing and resource utilisation.[82] In contrast, darolutamide does not require the thyroid function tests, reducing the need for extra lab tests and streamlining the monitoring process.[82] Furthermore, due to its lower number of DDIs, darolutamide is not associated with delays in treatment initiation that may occur with apalutamide, where additional steps are necessary to ensure patient safety. Such delays could incur extra healthcare costs, or the need for alternative treatments for their ongoing comorbidities.

Additionally, darolutamide is associated with better tolerability compared to apalutamide (see Section B.4.2.5). This is further supported by the NMA safety results, which suggest a preference for darolutamide + ADT over apalutamide + ADT, with fewer patients discontinuing treatment with darolutamide + ADT due to adverse events (Section B.3.9.3.3). The improved tolerability associated with darolutamide may help reduce healthcare resource utilisation, including doctor visits, hospitalisations, and additional treatments required for managing side effects. While these benefits may lead to reduced overall monitoring and healthcare resource utilisation costs, they were not included in the cost-comparison analysis. Therefore, the analysis assumes no differences in treatment monitoring and managing adverse events between darolutamide and apalutamide, reflecting a conservative approach.

The only difference between darolutamide and apalutamide included in the analysis are drug acquisition costs, with all other costs (such as drug administration, healthcare resource use, subsequent treatments, and adverse event costs) assumed to be similar for both treatments, which, as noted above, may not fully reflect the economic benefits of darolutamide with ADT versus apalutamide with ADT in the treatment of mHSPC.

B.4.2 Cost-comparison analysis inputs and assumptions

B.4.2.1 Features of the cost-comparison analysis

A simple cost comparison was carried out in Microsoft Excel® to evaluate the drug cost to the NHS associated with the use of darolutamide + ADT versus apalutamide + ADT in the treatment of adults with mHSPC.

The drug acquisition costs are calculated based on the time on treatment (ToT) data, which is informed by the ARANOTE trial for darolutamide + ADT. The same ToT is assumed for apalutamide + ADT in the analysis. Additionally, other efficacy outcomes as well as safety outcomes for both darolutamide + ADT and apalutamide + ADT are assumed to be equivalent. However, as mentioned in Section B.4.1, darolutamide + ADT is associated with better tolerability than apalutamide + ADT (more details in Section B.4.2.5) and assuming similar safety profiles for both treatments is a conservative approach.

The model uses a 28-day cycle length and assumes a lifetime time horizon (25 years), which is sufficient to capture the plausible maximum life expectancy for the ARANOTE ITT population (mean age 69 years). Shorter time horizons are explored in the scenario analysis in Section B.4.4.

The analysis is conducted from the perspective of the National Health Service (NHS) and personal social services (PSS) in England and Wales.

In line with the NICE cost-comparison user guide, the cost-comparison analysis includes costs associated with drug acquisition.[158] All other costs (monitoring, subsequent treatment, adverse events and end of life care costs) are conservatively assumed to be the same between darolutamide + ADT and apalutamide + ADT. Therefore, these are excluded from the analysis. As both drugs are administered orally and for the same duration of treatment, no difference in drug administration costs is expected.

The drug acquisitions costs are discounted at an annual rate of 3.5% in line with the NICE methods and process guide.[153] No discounting is considered in the scenario analysis as per the NICE cost-comparison user guide (Section B.4.4).[158]

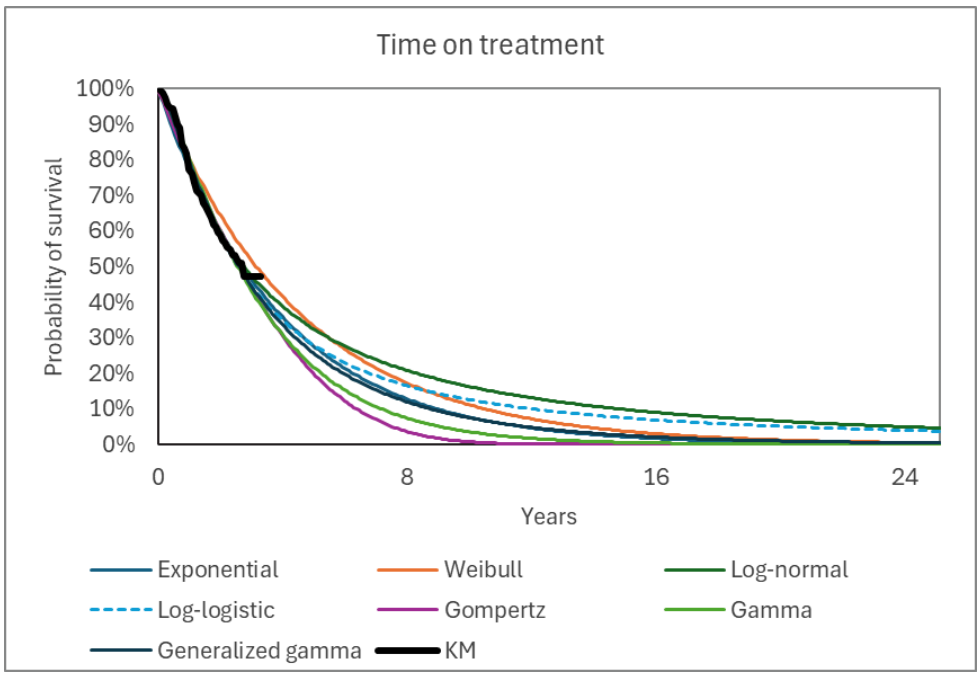
Mortality is not considered within the analysis as it is not expected to differ for patients receiving darolutamide versus apalutamide.

B.4.2.2 Time on treatment (ToT)

Drug acquisition costs are multiplied by the proportion of patients on treatment in each cycle, which is informed by the ARANOTE trial. Standard parametric models (exponential, Weibull, log-normal, log-logistic, Gompertz, and generalized gamma) were fitted to the darolutamide + ADT ToT KM data.

Figure 12 presents the standard parametric curves for darolutamide + ADT compared with the observed KM data from ARANOTE across the trial period and the model time horizon. The corresponding AIC values are presented in Table 31. Based on AIC (minimum) and the fit to the observed KM data, the log-logistic curve provides the best fit across all parametric curves and is therefore used in the base case analysis. The use of gamma and generalized gamma are explored in the scenario analysis, as the associated AIC values are within 5 points difference and the results of these scenario analyses are presented in Section B.4.4.

Figure 12: Standard parametric survival models – ToT (darolutamide + ADT and apalutamide + ADT)



Abbreviations: ADT: Androgen Deprivation Therapy; KM: Kaplan Meier; ToT: time on treatment.

Table 31: ToT AIC ranking

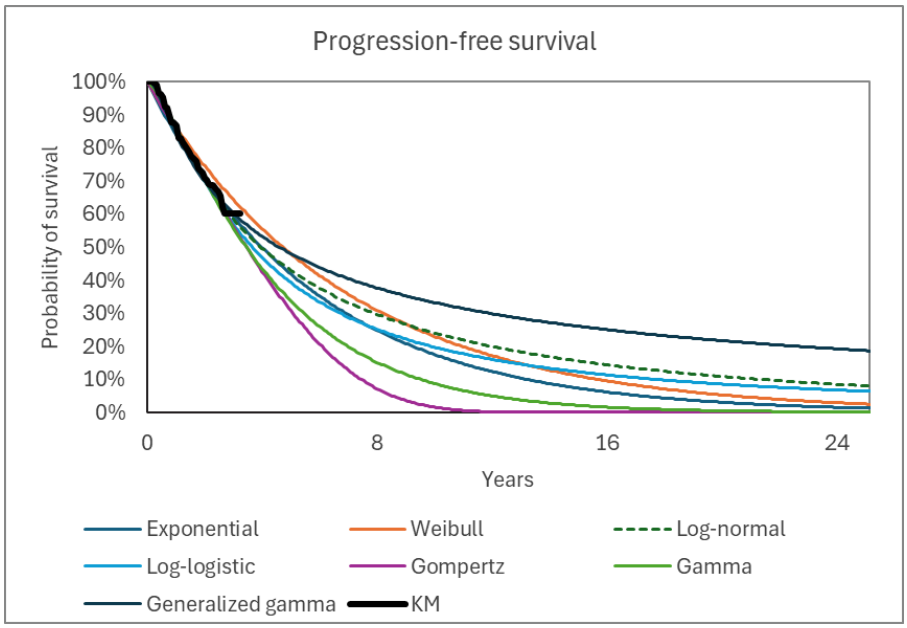
Distribution	AIC
Exponential	958.57
Weibull	951.49
Log-normal	956.84
Log-logistic	**945.84**
Gompertz	958.44
Gamma	949.94
Generalized gamma	950.07

Base case curve selections are in bold.

Abbreviations: AIC: Akaike Information Criterion; ToT: time on treatment.

A scenario analysis was conducted where drug costs were adjusted based on rPFS, instead of ToT, assuming that all patients will be treated up to progression or death, whichever occurs first. Figure 13 presents the standard parametric curves for darolutamide + ADT compared with the observed KM rPFS (Table 32), and based on AIC and visual fit, a log-normal curve was selected. The results of this scenario analysis are presented in Section B.4.4.

Figure 13: Standard parametric survival models – rPFS (darolutamide + ADT and apalutamide + ADT)



Abbreviations: ADT: Androgen Deprivation Therapy; KM: Kaplan Meier; rPFS: radiographic progress-free survival.

Table 32: rPFS AIC ranking

Distribution	AIC
Exponential	704.63
Weibull	699.03
Log-normal	**690.30**
Log-logistic	696.23
Gompertz	704.65
Gamma	697.67
Generalized gamma	690.57

Selected curve is in bold.

Abbreviations: AIC, Akaike Information Criterion; rPFS: radiographic progress-free survival.

B.4.2.3 Intervention and comparators' acquisition costs

Drug acquisition costs are calculated based on dosing regimens, dose intensity, unit costs, and ToT.

ToT data for darolutamide are sourced from the ARANOTE patient-level data and the same data is applied to apalutamide due to the absence of ToT data for apalutamide. The methods used to estimate the ToT data are described in Section B.4.2.2.

The recommended dose is 600 mg darolutamide (two film-coated tablets of 300 mg) taken orally twice daily, equivalent to a total daily dose of 1200 mg, as per the license.[126] The list price for a pack of 112 (300 mg) tablets of darolutamide is £4,040, equating to a cost per dose of £72.14 based on the BNF.[156] The model also takes into account a confidential discount of [redacted] applied as a simple discount on the price per pack, resulting in a modelled cost per dose of £[redacted].

The recommended dose of apalutamide is 240 mg (four 60 mg tablets) as an oral single daily dose according to the license.[127] A confidential PAS is approved for apalutamide in mHSPC. However, as this is unknown, the cost of apalutamide is modelled based on the list price shown from the BNF. The list price for a pack of 112 tablets is £2,735 as per the BNF.[157]

List prices from the BNF were also used to inform the cost of ADT in this analysis, where patients could receive leuprorelin (30.0%), goserelin (30.0%), or triptorelin (40.0%).[159] However, the drug acquisition cost of ADT is not included in this section, as it remains the same in both arms (due to the same time on treatment) and will cancel out when calculating the incremental results.

Drug doses are calculated by multiplying by the dose intensity. However, in the absence of dose intensity data for darolutamide + ADT and apalutamide + ADT, relative dose intensity was assumed to be 100% darolutamide and apalutamide in this analysis. Drug acquisition costs for darolutamide and apalutamide are provided in Table 33 with other relevant information.

Table 33: Acquisition costs of the intervention and comparator technologies

	Darolutamide SPC[126]	**Apalutamide** SPC[127]
Pharmaceutical formulation	300 mg tablets, 112 per pack	60 mg tablets, 112 per pack
(Anticipated) care setting	Secondary	Secondary
Acquisition cost (excluding VAT) – based on BNF[12, 23]	List price: £4,040 PAS price: £[redacted] (representing a simple discount of [redacted]%)	List price: £2,735
Method of administration	Oral	Oral
Doses	600 mg	240 mg
Dosing frequency	Twice daily	Once daily
Dose adjustments	If a patient experiences a ≥ Grade 3 toxicity or an intolerable adverse reaction related to darolutamide, dosing should be withheld or reduced to 300 mg twice daily until symptoms improve. Treatment may then be resumed at a dose of 600 mg twice daily.	If a ≥ Grade 3 toxicity or an intolerable adverse reaction is experienced by the patient, dosing should be held rather than permanently discontinuing treatment until symptoms improve to ≤ Grade 1 or original grade, then should be resumed at the same dose or a reduced dose (180 mg or 120 mg), if warranted
Average length of a course of treatment	Continuous until disease progression or unacceptable toxicity.	Continuous until disease progression or unacceptable toxicity.
Average cost of a course of treatment (acquisition costs only)	List price: £214,613 PAS price: £[redacted]	£146,539
(Anticipated) average interval between courses of treatment	N/A - continuous treatment	N/A - continuous treatment
(Anticipated) number of repeat courses of treatment	N/A	N/A

Abbreviations: BNF: British National Formulary; mg: milligram; PAS: Patient access scheme; SPC: Summary of Product Characteristics; VAT: value tax added.

B.4.2.4 Intervention and comparators' healthcare resource use and associated costs

Oral drug administration costs were assumed to be zero for darolutamide and apalutamide. The administration routes for ADT components - leuprorelin, goserelin, and triptorelin - are subcutaneous or intramuscular injections. The intramuscular injections were estimated to cost £545, while subcutaneous injections were estimated

to cost £412, as per the National Schedule of NHS Costs.[160] However, drug administration costs netted out in the model due to assuming the same rate of disease progression and ToT between darolutamide and apalutamide.

HCRU costs were assumed to be comparable between darolutamide + ADT and apalutamide + ADT; however, this is a conservative approach as darolutamide offers several benefits over apalutamide. As indicated earlier in Section B.1.3.2, patients with mHSPC often have multiple comorbidities requiring polypharmacy.[7-10] This leads to a significant risk of DDIs with apalutamide, which has potential of 310 known DDIs, as reported by the BNF.[11] Darolutamide is known to have fewer than 45 potential interactions and suggests use of darolutamide will mean easier monitoring and patient management.[12] The reduced DDIs associated with darolutamide, simplifies treatments decisions and reduces the need for coordination between healthcare providers needed for associated medication changes as the process often involves the engagement of general practitioners, hospital pharmacists, and consultant oncologists, which can be time-consuming and burdensome.[82] This aligns with the feedback from the UK clinicians during the HEOR advisory board meeting held in February 2025, where they highlighted several resource use benefits associated with darolutamide compared with apalutamide.[82]

Furthermore, the use of apalutamide is to be avoided in combination with relugolix, a newer oral ADT.[13, 14] As an oral GnRH antagonist, relugolix presents a potentially less resource-intensive alternative to traditional ADT, which typically involves injectable agents requiring clinic-based administration and associated healthcare resources such as staff time, procedural costs, and cold-chain logistics. In contrast, relugolix allows for self-administration, potentially reducing the burden on healthcare infrastructure and improving patient convenience. This advantage further supports the use of darolutamide, as relugolix can be co-administered with darolutamide, unlike apalutamide.

Additionally, the clinicians highlighted that patients receiving apalutamide require thyroid function tests as part of their treatment monitoring, adding another layer of testing and resource utilisation.[82] In contrast, darolutamide does not require the thyroid function tests, reducing the need for extra lab tests and streamlining the

monitoring process.[82] Furthermore, due to its lower number of DDIs, darolutamide is not associated with delays in treatment initiation that may occur with apalutamide, where additional steps are necessary to ensure patient safety. Such delays could incur extra healthcare costs, or the need for alternative treatments for their ongoing comorbidities.

B.4.2.5 Adverse reaction unit costs and resource use

As noted earlier in Section B.3.11.1, darolutamide is better tolerated than apalutamide. This is validated by the NMA results on safety outcomes, which favour darolutamide + ADT over apalutamide + ADT, though the evidence for a significant difference is not strong (Section B.3.9.3.3). However, the NMA results for discontinuation due to AEs show evidence of a difference in favour of darolutamide + ADT over apalutamide + ADT Section B.3.9.3.5).

To further explore the difference, the AEs associated with darolutamide + ADT in the ARANOTE trial were compared to those of apalutamide + ADT in the TITAN trial.[1, 3] As shown in Table 34, darolutamide, when compared naively to apalutamide, demonstrated a lower incidence of AEs that can impact a patient's daily life, such as fatigue, rash, falls, fractures, and hot flushes.[1, 3] This was reinforced by UK clinicians during the HEOR advisory board meeting that common AEs associated with apalutamide include fatigue, pain in extremities, and rash.[82]

Table 34: Summary of adverse events for darolutamide + ADT and apalutamide + ADT

Adverse event, n (%)	Darolutamide + ADT (n=445)	Apalutamide + ADT (n=524)
Any AE	405 (91.0)	507 (96.8)
Serious AE	105 (23.6)	104 (19.8)
Grade 3 or 4 AE	137 (30.8)	221 (42.2)
AE leading to permanent discontinuation of study drug	27 (6.1)	42 (8.0)
AEs of special interest – all grades		
Hot flushes	41 (9.2)	119 (22.7)
Rash	19 (4.3)	142 (27.1)
Falls	6 (1.3)	39 (7.4)
Fracture	18 (4.0)	33 (6.3)
Fatigue	25 (5.6)	103 (19.7)

Abbreviations: ADT: Androgen Deprivation Therapy; AEs: Adverse events.

Clinicians also noted that use of apalutamide is associated with hypothyroidism and atrial fibrillation.[82] One clinician mentioned that approximately 1 in 5 patients over the age of 50 have atrial fibrillation, which means many are on direct oral anticoagulants (DOACs).[82] Additionally, clinicians noted that from experience using darolutamide in other indications, highlighting its distinctiveness from other AR inhibitors due to its superior tolerability. Based on the findings from the ITC and the overall summary of adverse events in the TITAN and ARANOTE trials, it can be assumed that the safety profile of darolutamide is similar to, or better than, that of apalutamide, reflecting feedback from clinicians during the HEOR advisory board meeting. As a result, the cost and resource use associated with adverse events have conservatively not been included in the cost-comparison analysis.

B.4.2.6 Miscellaneous unit costs and resource use

No additional costs or resource use are associated with meaningful differences. Therefore, they have been excluded in accordance with the NICE cost-comparison user guide.[158]

B.4.2.7 Clinical expert validation

The assumption of equivalent efficacy between darolutamide + ADT and apalutamide + ADT was confirmed by UK clinical experts during the advisory board. The experts

noted that the patient populations for both treatments would be very similar in terms of disease status, age, and co-morbidities. One clinician commented positively on the ARANOTE population, highlighting it as one of the few studies with a diverse cohort, including Asian and Black men, and demonstrating efficacy in a wide range of patients, meaning that the ARANOTE trial is more in line with the UK clinical population than the equivalent trials for apalutamide and enzalutamide.

Clinicians also shared their experience using darolutamide in other indications, noting that it to be distinct from alternative AR inhibitors due to its superior tolerability. They further mentioned that apalutamide would likely result in higher resource utilisation due to its safety profile and has more DDIs compared to darolutamide.

B.4.2.8 Uncertainties in the inputs and assumptions

The key assumption underpinning the cost-comparison analysis is based on the anticipated equivalent outcomes for darolutamide + ADT and apalutamide +ADT in mHSPC. As shown in Section B.3.9.3 the NMA found no evidence of a difference in rPFS and OS between darolutamide + ADT and apalutamide + ADT was found.

Extrapolation methods often introduce uncertainty in oncology appraisals. Therefore, alternative ToT extrapolations are considered in the scenario analysis.

Additionally, scenario analyses were conducted to explore uncertainty in the cost-comparison analysis, including adjustments to drug acquisition costs based on rPFS, no discounting of future costs, and scenarios with short time horizons of 10 and 15 years. Lastly, there is uncertainty around the price of apalutamide due to the presence of a confidential PAS for its current indication, although the PAS price is unknown.

B.4.3 Base-case results

Base case results for the cost-comparison analysis between darolutamide + ADT and apalutamide +ADT are presented in Table 35 using the simple discount PAS price of £[redacted] for darolutamide.

Darolutamide + ADT is associated with cost savings per patient of £[redacted] across the model time horizon (25-years) based on the drug acquisition costs of £[redacted] for darolutamide and £146,539 for apalutamide (Table 35).

Table 35: Base case results with PAS price – cost-comparison analysis

	Darolutamide + ADT	Apalutamide + ADT	Difference
Acquisition costs	£[redacted]	£146,539	-£[redacted]

Abbreviations: ADT: Androgen Deprivation Therapy; PAS: Patient Access Scheme.

Base case results for the cost-comparison analysis between darolutamide and apalutamide are presented in Table 36 using the list price of £4,040 for darolutamide. Over 25 years, the expected total cost of darolutamide + ADT and apalutamide + ADT are estimated as £214,613 and £146,539, respectively. The cost difference between the two treatments was estimated to be £68,073.

Table 36: Base case results with list price – cost-comparison analysis

	Darolutamide + ADT	Apalutamide + ADT	Difference
Acquisition costs	£214,613	£146,539	£68,073

Abbreviations: ADT: Androgen Deprivation Therapy.

B.4.4 Scenario analyses

Scenario analyses were conducted to examine the uncertainty around the base case assumptions and test the robustness of the results. The results of the scenario analyses are presented in Table 37 using the simple discount PAS price of £[redacted] per for darolutamide and in Table 38 using the list price of £4,040.

The results suggest that the conclusion remains consistent across all scenarios i.e., darolutamide + ADT is cost saving when the PAS price is applied. The results were sensitive to the application of rPFS and alternative distributions of ToT.

Table 37:**Scenario analyses results – Darolutamide + ADT versus Apalutamide + ADT based on PAS price**

Label	Base case	Scenario	Incremental cost	% change from base case
Base case:			**-£[redacted]**	
Time horizon	25 years	10 years	-£[redacted]	-14.6%
		15 years	-£[redacted]	-6.7%
Discounting	3.5%	No discounting	-£[redacted]	+19.63%
Alternative ToT extrapolations	Log-logistic	Gamma	-£[redacted]	-22.83%
		Generalised gamma	-£[redacted]	-13.79%
Drug cost adjustments	Based on ToT	Based on rPFS	-£[redacted]	+40.5%

Abbreviations: ADT: androgen deprivation therapy; PAS: Patient access scheme; rPFS: radiographic progression-free survival; ToT: Time on treatment.

Table 38:**Scenario analyses results – Darolutamide + ADT versus Apalutamide + ADT based on list price**

Label	Base case	Scenario	Incremental cost	% change from base case
Base case:			**£68,073**	
Time horizon	25 years	10 years	£58,125	-14.6%
		15 years	£63,480	-6.7%
Discounting	3.5%	No discounting	£81,433	+19.63%
Alternative ToT extrapolations	Log-logistic	Gamma	£52,534	-22.83%
		Generalised gamma	£58,683	-13.79%
Drug cost adjustments	Based on ToT	Based on rPFS	£95,651	+40.5%

Abbreviations: ADT: androgen deprivation therapy; PAS: Patient access scheme; rPFS: radiographic progression-free survival; ToT: Time on treatment.

B.4.5 Benefits not captured in the analysis

Darolutamide and apalutamide are both ARTAs, but there are several potential benefits of darolutamide over apalutamide, based on clinical data and their pharmacological properties, which are not captured in the cost-comparison analysis. These include:

1. **Improved Safety Profile:** During both advisory board meetings, clinicians noted that darolutamide has better tolerability compared to apalutamide.[80, 82] This is further supported by the NMA results on safety data and discontinuation due to AEs (Sections B.3.9.3.3 and B.3.9.3.5).

2. **Reduced healthcare resource utilisation:** Darolutamide can improve healthcare resource utilisation by streamlining the management of mHSPC compared with existing ARTA. As mentioned by UK clinicians during the advisory board meeting that initiating treatment with existing ARIs can be resource-intensive, especially when there is a need to change concomitant medications due to high numbers of DDIs. They explained that, typically, the process involves the GP contacting the hospital pharmacist, who may need to draft a letter to ensure that the new medication is prescribed safely. In some cases, this letter must be authorised by the consultant oncologist to allow the patient to begin the new medication. This multistep process introduces several time-consuming steps for healthcare practitioners, potentially delaying the initiation of treatment in the primary care setting. The need for additional coordination between primary and secondary care providers can burden the healthcare system, requiring significant effort and resources. In contrast, darolutamide is associated with a low risk of DDIs. Recent evidence shows combining the new oral ADT, relugolix, with darolutamide is both feasible and effective in maintaining castrate testosterone levels without significant DDIs, whereas combining it with apalutamide should be avoided.[14, 161] As a result, the reduced number of DDIs with darolutamide is expected to reduce the burden on healthcare resources compared to other ARTIs.

3. **No additional monitoring:** Another point raised by the clinicians was the requirement for thyroid function tests in patients treated with apalutamide. This adds an additional layer of monitoring and complexity to their treatment regimen. This requirement increases the burden on healthcare resources, as it involves additional testing, follow-up appointments, and coordination between healthcare providers. The process requires the healthcare team to track thyroid levels, manage any necessary interventions, and ensure that patients continue to receive appropriate care, which can be time-consuming and resource intensive. In contrast, darolutamide does not require this level of additional monitoring, simplifying the management of patients and reducing the need for extra appointments or tests.

4. **Patient reported outcomes (PRO):** While consideration of the impact of darolutamide + ADT on patient's HRQoL is out of scope for the cost-comparison analysis, it should be noted there is evidence that darolutamide + ADT provide additional patient benefit to apalutamide + ADT. Through the NMA of time to deterioration in Functional Assessment of Cancer Therapy – Prostate (FACT-P) score, it was shown there to be strong evidence of shorter time to deterioration in FACT-P for patients receiving apalutamide + ADT then darolutamide + ADT (HR = [redacted]), which could reflect a better HRQoL for darolutamide + ADT compared to apalutamide + ADT.

B.4.6 Interpretation and conclusions of economic evidence

The cost-comparison analysis highlights that darolutamide + ADT generates a significant cost savings of £[redacted] per patient compared with apalutamide + ADT over the model time horizon (25 years), using the proposed PAS for darolutamide. Cost savings are achieved through the lower acquisition costs for darolutamide (£[redacted] cost per pack) and darolutamide + ADT remains cost saving across all the scenario analyses when PAS price is considered.

Beyond the cost savings, darolutamide offers additional benefits, particularly, a better safety profile, including a lower incidence of CNS related AEs that impact patients' day to day life. Darolutamide + ADT also has the potential to reduce healthcare resource

utilisation compared with apalutamide + ADT. Managing patients on existing AR inhibitors such as apalutamide can be resource intense due to high levels of DDI which can require treatment changes to medications for comorbidities in order to initiate anti-cancer treatment. These treatment changes can involve a multi-step process and coordination across multiple healthcare providers. This not only increases the workload of healthcare providers but also places a strain on the healthcare system and can delay treatment initiation.

Additionally, patients treated with apalutamide require thyroid function tests, adding extra monitoring steps and increasing healthcare resource utilisation. This involves additional tests, follow-ups, and coordination between healthcare providers. In contrast, darolutamide does not require this level of monitoring, simplifying patient management and reducing the need for extra appointments or tests.

By offering a treatment option with fewer contraindications and better tolerability, such as darolutamide, the need for extensive coordination and changes to concomitant medications may be reduced. This could simplify the treatment pathway, reduce delays, and ultimately lead to improved efficiency in patient care. Additionally, it could free up healthcare resources to focus on other critical aspects of care, enhancing overall healthcare system efficiency.

Finally, darolutamide + ADT has shown improved patient-reported quality of life and functional outcomes compared with apalutamide + ADT, as evidenced by the results of the NMA.

In conclusion, darolutamide + ADT offers not only substantial cost savings at the PAS price but may also enhance safety, convenience, and reduced use of healthcare resources compared to apalutamide, leading to better healthcare resource utilisation and improved patient outcomes.

B.5 References

1. Chi KN, Agarwal N, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, et al. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med. 2019;381(1):13-24.
2. Armstrong AJ, Szmulewitz RZ, Petrylak DP, Holzbeierlein J, Villers A, Azad A, et al. ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men With Metastatic Hormone-Sensitive Prostate Cancer. J Clin Oncol. 2019;37(32):2974-86.
3. Saad F, Vjaters E, Shore M, Olmos D, Xing N, Pereira de Santana Gomes AJ, et al. Darolutamide in Combination With Androgen-Deprivation Therapy in Patients With Metastatic Hormone-Sensitive Prostate Cancer From the Phase III ARANOTE Trial. ESMO September 16, 2024. J Clin Oncol. 2024; 00:1-11.
4. Bayer. Clinical Study Report: Phase 3 study of darolutamide in addition to ADT versus placebo plus ADT in men with mHSPC (ARANOTE). 2024.
5. Bayer AG. Clinical Study Report: Phase 3 study of darolutamide + docetaxel + ADT versus placebo + ADT in men with mHSPC (ARASENS).
6. Fizazi K, Shore N, Tammela TL, Ulys A, Vjaters E, Polyakov S, et al. Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med. 2019;380(13):1235-46.
7. Cancer Research UK. Risks and causes of prostate cancer 2022 [updated 18 May 2022. Available from: https://www.cancerresearchuk.org/about-cancer/prostate-cancer/risks-causes.
8. Benzo RM, Moreno PI, Fox RS, Silvera CA, Walsh EA, Yanez B, et al. Comorbidity burden and health-related quality of life in men with advanced prostate cancer. Support Care Cancer. 2023;31(8):496.
9. Goebell PJ, Raina R, Chen S, Rege S, Shah R, Grossman JP, Waldeck AR. Real-world treatment of metastatic hormone-sensitive prostate cancer in the USA, Europe and Asia. Future Oncol. 2024.
10. Lu-Yao G, Nightingale G, Nikita N, Keith S, Gandhi K, Swartz K, et al. Relationship between polypharmacy and inpatient hospitalization among older adults with cancer treated with intravenous chemotherapy. Journal of Geriatric Oncology. 2020;11(4):579-85.
11. BNF. British National Formulary: Apalutamide drug interactions 2025 [Available from: https://bnf.nice.org.uk/interactions/apalutamide/.
12. BNF. British National Formulary: Darolutamide drug interactions 2025 [Available from: https://bnf.nice.org.uk/interactions/darolutamide/.
13. BNF. Relugolix Drug Monograph: Interactions [Available from: https://bnf.nice.org.uk/interactions/relugolix/.
14. EMA. Summary of Product Characteristics: relugolix (Orgovyx 120 mg film-coated tablets) 2022 [updated 29 April Available from: https://www.ema.europa.eu/en/documents/product-information/orgovyx-epar-product-information_en.pdf.
15. Moilanen AM, Riikonen R, Oksala R, Ravanti L, Aho E, Wohlfahrt G, et al. Discovery of ODM-201, a new-generation androgen receptor inhibitor targeting resistance mechanisms to androgen signaling-directed prostate cancer therapies. Sci Rep. 2015;5:12007.

16. Fizazi K, Shore N, Tammela TL, Ulys A, Vjaters E, Polyakov S, et al. Nonmetastatic, Castration-Resistant Prostate Cancer and Survival with Darolutamide. N Engl J Med. 2020;383(11):1040-9.
17. Pubchem. Compound ID: 15951529.Accessed: June 10, 2024.
18. PubChem. Compound ID: 67171867. Accessed: June 10, 2024.
19. PubChem. Compound ID: 24872560.Accessed: June 10, 2024.
20. Zurth C, Sandman S, Trummel D, Seidel D, Nubbemeyer R, Gieschen H. Higher blood–brain barrier penetration of [14C]apalutamide and [14C]enzalutamide compared to [14C]darolutamide in rats using whole-body autoradiography. Genitourinary Cancers Symposium. Prostate Cancer-Advanced Disease. February 26, 2019. J Clin Oncol. 2019;37.
21. Williams SCR, Mazibuko N, O'Daly O, Zurth C, Patrick F, Kappeler C, et al. Comparison of Cerebral Blood Flow in Regions Relevant to Cognition After Enzalutamide, Darolutamide, and Placebo in Healthy Volunteers: A Randomized Crossover Trial. Target Oncol. 2023;18(3):403-13.
22. Crawford ED, Stanton W, Mandair D. Darolutamide: An Evidenced-Based Review of Its Efficacy and Safety in the Treatment of Prostate Cancer. Cancer Manag Res. 2020;12:5667-76.
23. BNF. British National Formulary: Enzalutamide drug interactions 2025 [Available from: https://bnf.nice.org.uk/interactions/enzalutamide/.
24. Appukkuttan S, Ko G, Fu C, Bannister B, Kong SX, Jhaveri J, Freedland SJ. Drug-drug interaction potential among patients with nonmetastatic castration-resistant prostate cancer (nmCRPC) treated with novel androgen receptor inhibitors. Expert Rev Anticancer Ther. 2024;24(5):325-33.
25. Baumgart SJ, Nevedomskaya E, Lesche R, Seidel H, Haendler B. A detailed comparison between second-generation AR antagonists reveals differences in the overall impact on gene regulation patterns in prostate cancer cells. Cancer Res. 2018;78:1798.
26. It’s a fact: prostate cancer now England’s most common cancer. [press release]. PCUK, 28 January 2025 2025.
27. Prostate Cancer UK: Prostate cancer statistics 2023 [updated August 2023. Available from: https://prostatecanceruk.org/for-health-professionals/data-and-evidence.
28. Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016;34(12):1402-18.
29. Scher HI, Solo K, Valant J, Todd MB, Mehra M. Prevalence of Prostate Cancer Clinical States and Mortality in the United States: Estimates Using a Dynamic Progression Model. PLoS One. 2015;10(10):e0139440.
30. Lowrance W, Dreicer R, Jarrard DF, et al. Advanced Prostate Cancer: AUA/SUO Guideline 2023 [Available from: https://www.auanet.org/guidelines-and-quality/guidelines/advanced-prostate-cancer.
31. Gillessen S, Bossi A, Davis ID, de Bono J, Fizazi K, James ND, et al. Management of patients with advanced prostate cancer-metastatic and/or castration-resistant prostate cancer: Report of the Advanced Prostate Cancer Consensus Conference (APCCC) 2022. Eur J Cancer. 2023;185:178-215.

32. Wenzel M, Preisser F, Hoeh B, Schroeder M, Würnschimmel C, Steuber T, et al. Impact of Time to Castration Resistance on Survival in Metastatic Hormone Sensitive Prostate Cancer Patients in the Era of Combination Therapies. Front Oncol. 2021;11:659135.
33. Appukkuttan S, Tangirala K, Babajanyan S, Wen L, Simmons S, Shore N. A Retrospective Claims Analysis of Advanced Prostate Cancer Costs and Resource Use. Pharmacoecon Open. 2020;4(3):439-47.
34. Hechmati G, Cure S, Gouépo A, Hoefeler H, Lorusso V, Lüftner D, et al. Cost of skeletal-related events in European patients with solid tumours and bone metastases: data from a prospective multinational observational study. J Med Econ. 2013;16(5):691-700.
35. Johanes C, Monoarfa RA, Ismail RI, Umbas R. Anxiety level of early- and late-stage prostate cancer patients. Prostate Int. 2013;1(4):177-82.
36. Saad F, Ivanescu C, Phung D, Loriot Y, Abhyankar S, Beer TM, et al. Skeletal-related events significantly impact health-related quality of life in metastatic castration-resistant prostate cancer: data from PREVAIL and AFFIRM trials. Prostate Cancer Prostatic Dis. 2017;20(1):110-6.
37. Hamid AA, Sayegh N, Tombal B, Hussain M, Sweeney CJ, Graff JN, Agarwal N. Metastatic Hormone-Sensitive Prostate Cancer: Toward an Era of Adaptive and Personalized Treatment. Am Soc Clin Oncol Educ Book. 2023;43:e390166.
38. Thomas C, Baunacke M, Erb HHH, Fussel S, Erdmann K, Putz J, Borkowetz A. Systemic Triple Therapy in Metastatic Hormone-Sensitive Prostate Cancer (mHSPC): Ready for Prime Time or Still to Be Explored? Cancers (Basel). 2021;14(1).
39. Agarwal N, McQuarrie K, Bjartell A, Chowdhury S, Pereira de Santana Gomes AJ, Chung BH, et al. Health-related quality of life after apalutamide treatment in patients with metastatic castration-sensitive prostate cancer (TITAN): a randomised, placebo-controlled, phase 3 study. Lancet Oncol. 2019;20(11):1518-30.
40. Stenzl A, Dunshee C, De Giorgi U, Alekseev B, Iguchi T, Szmulewitz RZ, et al. Effect of Enzalutamide plus Androgen Deprivation Therapy on Health-related Quality of Life in Patients with Metastatic Hormone-sensitive Prostate Cancer: An Analysis of the ARCHES Randomised, Placebo-controlled, Phase 3 Study. Eur Urol. 2020;78(4):603-14.
41. Chi KN, Protheroe A, Rodriguez-Antolin A, Facchini G, Suttman H, Matsubara N, et al. Patient-reported outcomes following abiraterone acetate plus prednisone added to androgen deprivation therapy in patients with newly diagnosed metastatic castration-naive prostate cancer (LATITUDE): an international, randomised phase 3 trial. Lancet Oncol. 2018;19(2):194-206.
42. Morgans AK, Chen YH, Sweeney CJ, Jarrard DF, Plimack ER, Gartrell BA, et al. Quality of Life During Treatment With Chemohormonal Therapy: Analysis of E3805 Chemohormonal Androgen Ablation Randomized Trial in Prostate Cancer. J Clin Oncol. 2018;36(11):1088-95.
43. Rush HL, Murphy L, Morgans AK, Clarke NW, Cook AD, Attard G, et al. Quality of Life in Men With Prostate Cancer Randomly Allocated to Receive Docetaxel or Abiraterone in the STAMPEDE Trial. J Clin Oncol. 2022;40(8):825-36.
44. Fizazi K, Smith MR, Hussan M, et al. Quality of life and patient-relevant endpoints with darolutamide in the phase 3 ARASENS study. ESMO Congress 2022; September 9-13, 2022; Paris, France2022.

45. Turco F, Di Prima L, Pisano C, Poletto S, De Filippis M, Crespi V, et al. How to Improve the Quality of Life of Patients with Prostate Cancer Treated with Hormone Therapy? Res Rep Urol. 2023;15:9-26.
46. Rencsok EM, Slopen N, McManus HD, Autio KA, Morgans AK, McSwain L, et al. Pain and Its Association with Survival for Black and White Individuals with Advanced Prostate Cancer in the United States. Cancer Res Commun. 2024;4(1):55-64.
47. Ito T, Grant L, Duckham BR, Ribbands AJ, Gater A. Qualitative and Quantitative Assessment of Patient and Carer Experience of Chemotherapy (Docetaxel) in Combination with Androgen Deprivation Therapy (ADT) for the Treatment of Metastatic Hormone-Sensitive Prostate Cancer (mHSPC). Adv Ther. 2018;35(12):2186-200.
48. Torvinen S, Färkkilä N, Sintonen H, Saarto T, Roine RP, Taari K. Health-related quality of life in prostate cancer. Acta Oncol. 2013;52(6):1094-101.
49. Prostate Cancer UK. Fatigue and prostate cancer factsheet.
50. Kretschmer A, van den Bergh RCN, Martini A, Marra G, Valerio M, Tsaur I, et al. Assessment of Health-Related Quality of Life in Patients with Advanced Prostate Cancer-Current State and Future Perspectives. Cancers (Basel). 2021;14(1).
51. Connor MJ, Genie MG, Burns D, Bass EJ, Gonzalez M, Sarwar N, et al. A Systematic Review of Patients' Values, Preferences, and Expectations for the Treatment of Metastatic Prostate Cancer. Eur Urol Open Sci. 2022;36:9-18.
52. Hall F, de Freitas HM, Kerr C, Ito T, Nafees B, Lloyd AJ, et al. Estimating utilities/disutilities for high-risk metastatic hormone-sensitive prostate cancer (mHSPC) and treatment-related adverse events. Qual Life Res. 2019;28(5):1191-9.
53. Appukkuttan S, Ko G, Fu C, Bannister B, Kong SX, Jhaveri J, Freedland SJ. Drug–drug interaction potential among patients with nonmetastatic castration-resistant prostate cancer (nmCRPC) treated with novel androgen receptor inhibitors. Expert Review of Anticancer Therapy.1-9.
54. National Cancer Institute (NCI). Cancer stat facts: Prostate cancer 2023 [Available from: https://seer.cancer.gov/statfacts/html/prost.html.
55. Parker C, Castro E, Fizazi K, Heidenreich A, Ost P, Procopio G, et al. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020;31(9):1119-34.
56. Cancer Research UK: Prostate cancer statistics [Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer#heading-Zero
57. Ozturan D, Morova T, Lack NA. Androgen Receptor-Mediated Transcription in Prostate Cancer. Cells. 2022;11(5).
58. Cornford P, Tilki D, van den Bergh RCN, Eberli D, De Meerleer G, De Santis M, et al. EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on Prostate Cancer. Arnhem, The Netherlands: EAU Guidelines Office; 2025.
59. CancerMPact® Treatment Architecture. Prostate Cancer, EU5. September 2023.
60. Cancer Research UK: Proportion of cancer cases by stage at diagnosis prostate cancer. Figures from 2018. 2024 [Available from: https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/.
61. Fizazi K, Gillessen S, clinicalguidelines@esmo.org EGCEa. Updated treatment recommendations for prostate cancer from the ESMO Clinical Practice

Guideline considering treatment intensification and use of novel systemic agents. Ann Oncol. 2023;34(6):557-63.
62. Fizazi K, Foulon S, Carles J, Roubaud G, McDermott R, Flechon A, et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 x 2 factorial design. Lancet. 2022;399(10336):1695-707.
63. Finianos A, Gupta K, Clark B, Simmens SJ, Aragon-Ching JB. Characterization of Differences Between Prostate Cancer Patients Presenting With De Novo Versus Primary Progressive Metastatic Disease. Clin Genitourin Cancer. 2017.
64. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med. 2017;377(4):352-60.
65. Iacovelli R, Ciccarese C, Caffo O, De Giorgi U, Tucci M, Mosillo C, et al. The prognostic value of pain in castration-sensitive prostate cancer. Prostate Cancer Prostatic Dis. 2020;23(4):654-60.
66. Francini E, Gray KP, Xie W, Shaw GK, Valenca L, Bernard B, et al. Time of metastatic disease presentation and volume of disease are prognostic for metastatic hormone sensitive prostate cancer (mHSPC). Prostate. 2018;78(12):889-95.
67. McDougall JA, Bansal A, Goulart BH, McCune JS, Karnopp A, Fedorenko C, et al. The Clinical and Economic Impacts of Skeletal-Related Events Among Medicare Enrollees With Prostate Cancer Metastatic to Bone. Oncologist. 2016;21(3):320-6.
68. Drudge-Coates L, Oh WK, Tombal B, Delacruz A, Tomlinson B, Ripley AV, et al. Recognizing Symptom Burden in Advanced Prostate Cancer: A Global Patient and Caregiver Survey. Clin Genitourin Cancer. 2018;16(2):e411-e9.
69. Chi KN, Chowdhury S, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, et al. Apalutamide in Patients With Metastatic Castration-Sensitive Prostate Cancer: Final Survival Analysis of the Randomized, Double-Blind, Phase III TITAN Study. J Clin Oncol. 2021;39(20):2294-303.
70. James C, Brunckhorst O, Eymech O, Stewart R, Dasgupta P, Ahmed K. Fear of cancer recurrence and PSA anxiety in patients with prostate cancer: a systematic review. Support Care Cancer. 2022;30(7):5577-89.
71. Boye M, Ribbands A, Leith A, Clayton E, Butcher J, Rybowski S. Real-world health-related quality of life and caregiver need in patients with metastatic hormone-sensitive and metastatic castration-resistant prostate cancer. Journal of Clinical Oncology. 2022;40(6_suppl):54-.
72. Dodkins J, Cook A, Mayne E, Parry M, Parry MG, Boyle J, et al. Are evidence-based guidelines translating into clinical practice? A national population-based study of the use of treatment intensification in metastatic hormone-sensitive prostate cancer (mHSPC) in England. Eur J Cancer. 2025;220:115335.
73. National Prostate Cancer Audit (NPCA). Patient Summary of NPCA 2024 State of the Nation. 2024.
74. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024;74(1):12-49.

75. Desai MM, Cacciamani GE, Gill K, Zhang J, Liu L, Abreu A, Gill IS. Trends in Incidence of Metastatic Prostate Cancer in the US. JAMA Netw Open. 2022;5(3):e222246.
76. National Prostate Cancer Audit (NPCA). NPCA Annual Report 2020 (updated: January 2021) 2021 [Available from: https://www.npca.org.uk/reports/npca-annual-report-2020/.
77. National Prostate Cancer Audit (NPCA). NPCA Annual Report 2021 (updated: January 2022) 2022 [Available from: https://www.npca.org.uk/reports/npca-annual-report-2020/.
78. Office for National Statistics. Cancer survival in England - adults diagnosed (2013 - 2017 dataset). Updated: 12 August 2019 2019 [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed.
79. Rane JK, Chowdhury A, Kinnaird W. Treatment of metastatic hormone sensitive prostate cancer. Trends in Urol Men's Health. 2021;12:7-10.
80. Bayer AG. ARANOTE Advisory Board Meeting: Understanding the future metastatic hormone sensitive prostate cancer (mHSPC) landscape. Bayer AG; 2024 6 December 2024.
81. NICE. NICE Guideline NG131: Prostate cancer: diagnosis and management. Published 9 May 2019. 2019 [updated 15 December 2021.
82. Bayer AG. NICE Advisory Board Meeting: Darolutamide in combinatino with ADT for the treatment of metastatic hormone sensitive prostate cancer. 11 Februrary 2025.; 2025.
83. Glen H, Bahl A, Clarke N, Jain S, Kalsi T, Khoo V, Mobeen J. A modified Delphi consensus regarding the clinical utility of triplet therapy in patients with metastatic hormone-sensitive prostate cancer patients in the UK (in press). 2024.
84. NICE. NICE Technology Appraisal TA741: Apalutamide with androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer – Technology appraisal guidance. October 28, 2021. 2021.
85. NICE. NICE Technology Appraisal TA412: Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases. Technology appraisal guidance. Published: 28 September 2016. 2016 [Available from: www.nice.org.uk/guidance/ta412.
86. NHS England. Clinical Commissioning Policy Statement: Docetaxel in combination with androgen deprivation therapy for the treatment of hormone naïve metastatic prostate cancer (B15/PS/a). Updated: 20 January 2016. [Available from: https://www.england.nhs.uk/wp-content/uploads/2016/01/b15psa-docetaxel-policy-statement.pdf?UNLID=106952065020223157562 4.
87. National Cancer Drugs Fund. National Cancer Drugs Fund List. Version 1.346. Accessed 7th February 2025 2025 [
88. Kyriakopoulos CE, Chen YH, Carducci MA, Liu G, Jarrard DF, Hahn NM, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer: Long-Term Survival Analysis of the Randomized Phase III E3805 CHAARTED Trial. J Clin Oncol. 2018;36(11):1080-7.
89. Smith MR, Hussain M, Saad F, Fizazi K, Sternberg CN, Crawford ED, et al. Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer. N Engl J Med. 2022;386(12):1132-42.

90. Docetaxel summary of product characteristics (SmPC). Sanofi-Aventis; December 2023.
91. Docetaxel prescribing information. Sanofi-Aventis; January 2023.
92. Mir NA, Akmal W, Imam M, Giurcanu M, Szmulewitz RZ, Stadler WM. Adverse outcomes (AOs) in patients (pts) with metastatic castration-sensitive prostate cancer (mCSPC) treated with intensified androgen deprivation therapy (ADT+). Journal of Clinical Oncology. 2024;42(4_suppl):113-.
93. Sandhu S, Moore CM, Chiong E, Beltran H, Bristow RG, Williams SG. Prostate cancer. Lancet. 2021;398(10305):1075-90.
94. James ND, Tannock I, N'Dow J, Feng F, Gillessen S, Ali SA, et al. The Lancet Commission on prostate cancer: planning for the surge in cases. Lancet. 2024;403(10437):1683-722.
95. Graham LS, Lin JK, Lage DE, Kessler ER, Parikh RB, Morgans AK. Management of Prostate Cancer in Older Adults. Am Soc Clin Oncol Educ Book. 2023;43:e390396.
96. Loh KP, Liposits G, Arora SP, Neuendorff NR, Gomes F, Krok-Schoen JL, et al. Adequate assessment yields appropriate care-the role of geriatric assessment and management in older adults with cancer: a position paper from the ESMO/SIOG Cancer in the Elderly Working Group. ESMO Open. 2024;9(8):103657.
97. Zheng J, Sampurno F, George DJ, Morgans AK, Nguyen H, Abrahm JL, et al. Establishing metastatic prostate cancer quality indicators using a modified Delphi approach. Clin Genitourin Cancer. 2022;20(2):e151-e7.
98. Conner T, Appukkuttan S, Kong S, Jhaveri J, Ko G, Kalayeh B, et al. Utilization of metastatic hormone sensitive prostate cancer (mHSPC) treatment in a community oncology practice setting. 2023 ASCO Genitourinary Cancers Symposium. J Clin Oncol. 2023;41:Abstract 86.
99. Leith A, Ribbands A, Kim J, Clayton E, Gillespie-Akar L, Yang L, Ghate SR. Impact of next-generation hormonal agents on treatment patterns among patients with metastatic hormone-sensitive prostate cancer: a real-world study from the United States, five European countries and Japan. BMC Urol. 2022;22(1):33.
100. Barata PC, Leith A, Ribbands A, Montgomery R, Last M, Arondekar B, et al. Real-World Treatment Trends Among Patients with Metastatic Castration-Sensitive Prostate Cancer: Results from an International Study. Oncologist. 2023;28(9):780-9.
101. NPCA. National Prostate Cancer Audit Quality Improvement Plan – September 2024. 2024.
102. El-Taji O, Taktak S, Jones C, Brown M, Clarke N, Sachdeva A. Cardiovascular Events and Androgen Receptor Signaling Inhibitors in Advanced Prostate Cancer: A Systematic Review and Meta-Analysis. JAMA Oncol. 2024;10(7):874-84.
103. Appukkuttan S, Yao J, Partridge J, Kong SX, Parkin J, Freedland SJ. Adverse events and costs among non-metastatic castration-resistant prostate cancer patients. Journal of Medical Economics. 2024;27:145-52.
104. Conde-Estévez D, Henríquez I, Muñoz-Rodríguez J, Rodriguez-Vida A. Treatment of non-metastatic castration-resistant prostate cancer: facing age-related comorbidities and drug–drug interactions. Expert Opinion on Drug Metabolism & Toxicology. 2022;18(9):601-13.
105. Boujonnier F, Lemaitre F, Scailteux L-M. Pharmacokinetic Interactions Between Abiraterone, Apalutamide, Darolutamide or Enzalutamide and

Antithrombotic Drugs: Prediction of Clinical Events and Review of Pharmacological Information. Cardiovascular Drugs and Therapy. 2023.
106. Park SJ, Yoder B, Li T. Comparison of second-generation antiandrogens for the treatment of prostate cancer. Journal of Hematology Oncology Pharmacy. 2022;12(2).
107. Leblanc K, Edwards SJ, Dranitsaris G, Leong DP, Carrier M, Malone S, et al. Drug Interactions between Androgen Receptor Axis-Targeted Therapies and Antithrombotic Therapies in Prostate Cancer: Delphi Consensus. Cancers (Basel). 2024;16(19).
108. Bolek H, Yazgan SC, Yekeduz E, Kaymakcalan MD, McKay RR, Gillessen S, Urun Y. Androgen receptor pathway inhibitors and drug-drug interactions in prostate cancer. ESMO Open. 2024;9(11):103736.
109. Shore N, Zurth, C., Fricke, R. et al. . Evaluation of Clinically Relevant Drug–Drug Interactions and Population Pharmacokinetics of Darolutamide in Patients with Nonmetastatic Castration-Resistant Prostate Cancer: Results of Pre-Specified and Post Hoc Analyses of the Phase III ARAMIS Trial. Targ Oncol. 2019;14:527–39.
110. Smith MR, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN, et al. Apalutamide and Overall Survival in Prostate Cancer. Eur Urol. 2021;79(1):150-8.
111. Gillessen S, Turco F, Davis ID, Efstathiou JA, Fizazi K, James ND, et al. Management of Patients with Advanced Prostate Cancer. Report from the 2024 Advanced Prostate Cancer Consensus Conference (APCCC). Eur Urol. 2025;87(2):157-216.
112. Armstrong AJ, Azad AA, Iguchi T, Szmulewitz RZ, Petrylak DP, Holzbeierlein J, et al. Improved Survival With Enzalutamide in Patients With Metastatic Hormone-Sensitive Prostate Cancer. J Clin Oncol. 2022;40(15):1616-22.
113. Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. N Engl J Med. 2015;373(8):737-46.
114. James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet. 2016;387(10024):1163-77.
115. Mir NA, Akmal W, Imam M, Giurcanu M, Russell Zelig Szmulewitz RZ, Stadler WM. Adverse outcomes (AOs) in patients (pts) with metastatic castration-sensitive prostate cancer (mCSPC) treated with intensified androgen deprivation therapy (ADT+). 2024 ASCO Genitourinary Cancers Symposium. January 29, 2024. J Clin Oncol. 2024;42.
116. Bayer AG. Final Overall Survival Results Summary for Study 21140 (ARANOTE): A randomized, double-blind, placebo-controlled Phase 3 study of darolutamide in addition to androgen deprivation therapy (ADT) versus placebo plus ADT in men with metastatic hormone-sensitive prostate cancer (mHSPC). Data cut-off: 16 Jan 2025.; 2025.
117. Aziz MK, Molony D, Monlezun D, Holder T, Brunckhorst O, Higgason N, et al. Prostate Cancer Therapy Cardiotoxicity Map (PROXMAP) for Advanced Disease States: A Systematic Review and Network Meta-analysis with Bayesian Modeling of Treatment Histories. Eur Urol. 2025;87(1):15-26.
118. Lyon AR, Lopez-Fernandez T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration

with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J Cardiovasc Imaging. 2022;23(10):e333-e465.
119. Daher R, Ruplin A, Gupta S, Spiess PE, Kamat AM, Cigliola A, et al. The spectrum of cutaneous toxicities related to novel genitourinary cancer therapies. Crit Rev Oncol Hematol. 2024;200:104420.
120. Almeida V, Pires D, Silva M, Teixeira M, Teixeira RJ, Louro A, et al. Dermatological Side Effects of Cancer Treatment: Psychosocial Implications-A Systematic Review of the Literature. Healthcare (Basel). 2023;11(19).
121. de Freitas HM, Ito T, Hadi M, Al-Jassar G, Henry-Szatkowski M, Nafees B, Lloyd AJ. Patient Preferences for Metastatic Hormone-Sensitive Prostate Cancer Treatments: A Discrete Choice Experiment Among Men in Three European Countries. Adv Ther. 2019;36(2):318-32.
122. Gonzalez JM, Ganguli A, Morgans AK, Tombal BF, Hotte SJ, Suzuki H, et al. Discrete-Choice Experiment to Understand the Preferences of Patients with Hormone-Sensitive Prostate Cancer in the USA, Canada, and the UK. Patient. 2023;16(6):607-23.
123. Menges D, Piatti MC, Omlin A, Cathomas R, Benamran D, Fischer S, et al. Patient and General Population Preferences Regarding the Benefits and Harms of Treatment for Metastatic Prostate Cancer: A Discrete Choice Experiment. Eur Urol Open Sci. 2023;51:26-38.
124. George DJ, Ganguli A, Morgans AK, et al. Patient preferences for treatment and outcomes in hormone-sensitive prostate cancer (HSPC). Journal of Clinical Oncology. 2022;40(16_suppl):e18757-e.
125. George DJ, Morgans AK, Constantinovici N, Khan N, Khan J, Chen G, et al. Androgen Receptor Inhibitors in Patients With Nonmetastatic Castration-Resistant Prostate Cancer. JAMA Netw Open. 2024;7(8):e2429783.
126. EMA. Summary of Product Characteristics. Daralutamide (NUBEQA) 2024 [updated 20-Dec-2024. Available from: https://www.medicines.org.uk/emc/product/11324/smpc/print.
127. EMA. Summary of Product Characteristics: apalutamide (Erleada) 2023 [updated 22 September 2023. Available from: https://www.ema.europa.eu/en/documents/product-information/erleada-epar-product-information_en.pdf#:~:text=Treatment%20with%20apalutamide%20should%20be%20initiated%20and%20supervised,mg%20tablets%29%20as%20an%20oral%20single%20daily%20dose.
128. EMA. Summary of Product Characteristics: enzalutamide (Xtandi) 2018 [updated 8 February 2018. Available from: https://www.ema.europa.eu/en/documents/product-information/xtandi-epar-product-information_en.pdf.
129. Number of UK people with heart rhythm condition rises by 50% in a decade [press release]. British Heart Foundation, 19 May 2023 2023.
130. NICE. Atrial fibrillation: How common is it? ; 2024 October 2024.
131. Pan Z, Xu X, Xu X, Wu S, Zhang Z, Liu S, et al. Prevalence and outcomes of atrial fibrillation in patients suffering prostate cancer: a national analysis in the United States. Front Cardiovasc Med. 2024;11:1382166.

132. Shore N, Garcia-Horton V, Terasawa E, Ayyagari R, Grossman JP, Waldeck AR. Safety Differences Across Androgen Receptor Inhibitors in Nonmetastatic Castration-Resistant Prostate Cancer. Future Oncology. 2023;19(5):385-95.
133. Wang L, Lu B, He M, Wang Y, Wang Z, Du L. Prostate Cancer Incidence and Mortality: Global Status and Temporal Trends in 89 Countries From 2000 to 2019. Front Public Health. 2022;10:811044.
134. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-49.
135. Vince RA, Jr., Jiang R, Bank M, Quarles J, Patel M, Sun Y, et al. Evaluation of Social Determinants of Health and Prostate Cancer Outcomes Among Black and White Patients: A Systematic Review and Meta-analysis. JAMA Netw Open. 2023;6(1):e2250416.
136. National Institute for Health and Care Excellence. Apalutamide with androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer [TA741]. Committee Discussion. 2021 [updated 28 October 2021. Available from: https://www.nice.org.uk/guidance/ta741/chapter/3-Committee-discussion#end-of-life.
137. Fizazi K, Shore N, Tammela TL, Ulys A, Vjaters E, Polyakov S, et al. Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med. 2019;380(13):1235-46.
138. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.
139. Halabi S, Roy A, Rydzewska L, Guo S, Godolphin P, Hussain M, et al. Radiographic Progression-Free Survival and Clinical Progression-Free Survival as Potential Surrogates for Overall Survival in Men With Metastatic Hormone-Sensitive Prostate Cancer. J Clin Oncol. 2024;42(9):1044-54.
140. National Institute for Health and Care Excellence. Darolutamide with androgen deprivation therapy and docetaxel for treating hormone-sensitive metastatic prostate cancer. Technology appraisal guidance [TA903]. 2023 [Available from: https://www.nice.org.uk/guidance/ta903.
141. Bahl A, Challapalli A, Das P. Prospective real world data evaluation of clinical outcomes in metastatic hormone sensitive prostate cancer (MHSPC) patients treated as part of triplet therapy with darolutamide: UK multicenter RECOMMEND study. J Clin Oncol. 2025;43(89).
142. Dias SW, N. Sutton, A. . NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. Report by the Decision Support Unit 2011 (last updated September 2016). 2011.
143. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Med Decis Making. 2013;33(5):607-17.
144. Bujkiewicz S, Achana F, Papanikos T, Riley RD, Keith R. NICE DSU technical support document 20: Multivariate meta-analysis of summary data for combining treatment effects on correlated outcomes and evaluating surrogate endpoints. 2019.
145. White IR. Multivariate random-effects meta-analysis. Stata. 2009;9:40-56.

146. Riley RD, Jackson D, Salanti G, Burke DL, Price M, Kirkham J, White IR. Multivariate and network meta-analysis of multiple outcomes and multiple treatments: rationale, concepts, and examples. BMJ. 2017;358:j3932.
147. Lunn D, Jackson C, Best N, Thomas A, Spiegelhalter D. The BUGS book. A practical introduction to Bayesian analysis, Chapman Hall, London. 2013.
148. Davis ID, Martin AJ, Stockler MR, Begbie S, Chi KN, Chowdhury S, et al. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. N Engl J Med. 2019;381(2):121-31.
149. Sternberg CN, Fizazi K, Saad F, Shore ND, De Giorgi U, Penson DF, et al. Enzalutamide and Survival in Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med. 2020;382(23):2197-206.
150. Sweeney CJ, Martin AJ, Stockler MR, Begbie S, Cheung L, Chi KN, et al. Testosterone suppression plus enzalutamide versus testosterone suppression plus standard antiandrogen therapy for metastatic hormone-sensitive prostate cancer (ENZAMET): an international, open-label, randomised, phase 3 trial. Lancet Oncol. 2023;24(4):323-34.
151. Higano C. Enzalutamide, apalutamide, or darolutamide: are apples or bananas best for patients? Nat Rev Urol. 2019;16(6):335-6.
152. Pajouhesh H, Lenz GR. Medicinal chemical properties of successful central nervous system drugs. NeuroRx. 2005;2(4):541-53.
153. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual. 2022.
154. National Institute for Health and Care Excellence. Darolutamide with androgen deprivation therapy for treating hormonesensitive metastatic prostate cancer. Final Scope. 2025 19 March 2025.
155. National Institute for Health and Care Excellence. Darolutamide with androgen deprivation therapy for treating hormone-relapsed non-metastatic prostate cancer. Technology appraisal guidance. [TA660] 2020 [Available from: https://www.nice.org.uk/guidance/ta660/chapter/1-Recommendations.
156. BNF. Darolutamide. Medicinal forms [Available from: https://bnf.nice.org.uk/drugs/darolutamide/medicinal-forms/.
157. BNF. Apalutamide. Medicinal forms [Available from: https://bnf.nice.org.uk/drugs/apalutamide/medicinal-forms/.
158. User guide for the cost comparison company evidence submission template. NICE process and methods [PMG32] [Internet]. 2017. Available from: https://www.nice.org.uk/process/pmg32/chapter/cost-comparison-analysis.
159. BNF. BNF Online. British National Formulary https://wwwbnforg. 2024.
160. NHS England. National Schedule of NHS Costs 2022/23. National Health Service. 2024.
161. Sonpavde GP, Moschovas M, Alemany CA, Sehgal R, Khan Q, Emtage J, et al. Neoadjuvant darolutamide and relugolix combination preceding radical prostatectomy for high risk localized and locally advanced prostate cancer: A phase I/Ib trial. Journal of Clinical Oncology. 2025;43(5_suppl):TPS433-TPS.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal: cost-comparison

Darolutamide with androgen deprivation therapy for treating metastatic hormone-sensitive prostate cancer [ID6452]

Summary of Information for Patients (SIP)

April 2025

File name	Version	Contains confidential information	Date
ID6452_darolutamide ADT mHSPC_SIP_[NO CON]	V1	No	17/04/25

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

UK approved name: Darolutamide **Brand name:** Nubeqa®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

The patient population being considered by NICE in this appraisal is adult men with metastatic hormone sensitive prostate cancer (mHSPC) who are unsuitable for chemotherapy (docetaxel). People with mHSPC include those who are newly diagnosed or with a previous diagnosis where the cancer has returned. mHSPC is a stage of prostate cancer where the cancer has spread from the prostate to other parts of the body, but it still responds to hormone therapy known as androgen deprivation therapy (ADT). Through surgery to remove the testicles, or drugs called LHRH agonists or GnRH antagonists (e.g., like leuprorelin, goserelin, triptorelin, histrelin, and degarelix), ADT lowers or blocks the individual's levels of testosterone to slow cancer growth. Although there is currently no cure for mHSPC, the goal of treatment is to help slow its progression and prolong life.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Darolutamide + ADT does not yet have marketing authorisation in the UK for treating mHSPC. Darolutamide + ADT was filed with the UK Medical and Healthcare products Regulatory Agency (MHRA) for this licence extension on 15th October 2024, with approval expected later in 2025.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Bayer has provided grant financial support to Tackle Prostate Cancer, to support their annual national conference in 2024 and 2025 respectively. We have also provided grant funding to support their 'Many Faces of Prostate Cancer' awareness campaign of peer-to-peer support for men living with prostate cancer, and for their partners and carers.

Bayer is working with Prostate Cancer Research on a collaborative research project on variations in prostate cancer treatment, due to report later in 2025. Our collaboration with Prostate Cancer Research also includes endorsement of their 'Proactive for Your Prostate' national screening programme policy campaign.

We have also collaborated with patient organisations (Prostate Cancer Research and Prostate Cancer UK) on a Bayer-led policy project highlighting inequalities in prostate cancer. This includes a service provision agreement with Prostate Cancer Research. Bayer collaborated with clinical and patient organisation representatives to seek their views and endorsement of our policy positions for this project, which were presented to MPs in Parliament.

Please note, the collaborations listed are in the last year only (from January 2024). All details of Bayer's relevant partnerships and transfers of value to patient organisations are listed on the Bayer website, linked here.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Prostate cancer is the most common cancer diagnosed in males in the UK, accounting for 28% of all new cancer cases in men in the UK (2017–2019).[1, 2] As many as 1 in 8 men will be diagnosed with prostate cancer in the UK, and over 10,000 men will die from prostate cancer each year in England.[3]

Risk factors for prostate cancer include older age (prostate cancer is most frequently diagnosed in males aged 65 to 74 years[4]), prostate-specific antigen (PSA) level, obesity, a family history of prostate cancer, and ethnicity.[5] The risk of developing prostate cancer is significantly higher in Black African males than in White or Asian males.[6]

The National Prostate Cancer Audit reported a total of 55,241 and 2,521 men were diagnosed with prostate cancer in England in 2023 and Wales in 2022, respectively, and also reported an increase of 9% in England and 26% in Wales each year.[7] Epidemiology data specifically on mHSPC are limited, but estimates suggest the rate of mHSPC is rising, including in patients of younger age (45–75 years).[8, 9] A total of 13% of new prostate cancer cases between 2018 and 2020 in England were classed as newly diagnosed mHSPC, with an estimated total of 7,213 cases of newly diagnosed mHSPC in the UK.[10, 11]

mHSPC disease-related symptoms are very common resulting in a significant clinical burden.[12-17] Patients frequently experience symptoms such as fatigue (73%), urinary symptoms (63%), sexual dysfunction (62%), and bone pain (52%).[18] Other common symptoms include difficulty sleeping,

weakness/numbness in extremities, and weight loss.[18] Disease-related symptoms and treatment-related side-effects, such as fatigue and rash, significantly reduce patients' quality of life,[19-23] while fear of worsening of the disease is linked to mental health symptoms, such as depression and anxiety.[24]

Fatigue is reported by patients and their healthcare providers (HCPs) as one of the most burdensome symptoms of mHSPC and has a large impact on a patient's quality of life (QoL). Fatigue makes it difficult for men to conduct ordinary activities of daily life, such as personal care, participating in social activities, and working.[25] This greatly impacts their ability to lead a productive and fulfilling life, causing emotional strain, and a greater need for supportive care.[19-21, 26] Treatments that are currently available for mHSPC frequently cause fatigue, including the second generation androgen-receptor targeted agents (ARTAs) apalutamide and enzalutamide.[25, 27-29]

Patients with mHSPC are generally older and often have other long term medical conditions that require ongoing treatment with other medications.[30, 31] Data suggests patients with prostate cancer can be taking an average of 10 medications, as well as their prostate cancer treatment.[31] This means there is increased risk of interactions between the drugs the patient is taking which makes decisions on the best treatment course for mHSPC more complex.[32] For example, the British National Formulary (BNF) reports there are 310 and 233 potential drug interactions for apalutamide and enzalutamide, including interactions with medications used to treat common conditions in patients with mHSPC, such as atrial fibrillation and hypertension.[33, 34]

Caregivers to patients living with mHSPC also experience considerable time and emotional burdens. A European study of 376 patients with metastatic prostate cancer, including patients in the UK, showed caregivers provided between 17–18 care-hours per week.[35]

mHSPC is a life-limiting disease. Patients with mHSPC will ultimately progress to metastatic castrate-resistant prostate cancer (mCRPC), the final clinical stage of prostate cancer. mCRPC is associated with poor survival, increased symptoms, a large deterioration in quality of life, and significant economic impact.[36-42] The overall median five-year survival rate is 86.6% for patients with prostate cancer, but, when diagnosed at a metastatic stage, the five-year survival rate drops to 49%.[4, 43] Reduced survival is mainly due to the progression of mHSPC to mCRPC.[44] As such, the most important treatment goal in mHSPC is delaying disease progression.[45, 46]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Diagnosis of prostate cancer aims for the timely detection of significant disease.[27] In men with raised levels of prostate specific antigen (PSA; a protein produced by the prostate that is linked to increased risk of prostate cancer when levels are above normal), a prostate cancer risk calculator based on a number of different medical factors and family history, and/or medical imaging determines whether there is a need for further diagnostic tests. A prostate biopsy, where a small sample of tissue is collected and analysed may be needed.[5] Together, these diagnostic tests determine whether the disease is localised or has spread i.e., is metastatic.[5,47]

The introduction of darolutamide + ADT does not require any additional diagnostic tests.

2c) Current treatment options:

An advisory board meeting with clinical experts in prostate cancer who practise in England and Wales confirmed that clinical guidelines from NICE, ESMO and EAU are followed for treating mHSPC.[22, 27, 48, 49] For several decades the use of ADT alone (ADT monotherapy) was the standard of care for mHSPC,[45] but up to date guidance recommends intensified combination treatment (with an ARTA in addition to ADT or darolutamide + ADT + docetaxel triplet therapy) because it is more effective.[50] Only a small percentage of patients in England and Wales with mHSPC receive ADT monotherapy (5–20%, varying among treatment centres) and use is restricted to those who are unable to tolerate intensified treatment, such as those who are very elderly, have widespread disease, and/or have multiple other medical conditions.[22, 48, 51, 52]

Current NICE guidance recommends combination treatment of mHSPC with ADT + docetaxel (NICE Clinical Guideline 131)[49]; however, this guidance is now outdated and clinicians have confirmed that ADT + docetaxel is no longer a standard of care.[22] ESMO guidelines followed by clinicians in England and Wales recommend triplet therapy with darolutamide + ADT + docetaxel or an ARTA + ADT to be used as initial (first line) treatment for mHSPC.[48] Triplet therapy was recommended based on its significant survival benefits over ADT + docetaxel observed in the phase III ARASENS study.[48] However, docetaxel kills healthy cells as well as cancerous ones and its use can cause multiple side effects, so it is not suitable for all patients.[53, 54] Currently, only 10–20% of patients England and Wales with mHSPC receive triplet therapy[22] Most patients in England and Wales with mHSPC receive ARTA (apalutamide or enzalutamide) + ADT doublet therapy (70–80%).[22] Clinical trials show combining ADT with an ARTA improves radiographic progression free survival (rPFS, i.e., the length of time during and after treatment that a patient lives without the disease worsening, as detected by imaging techniques) and overall survival in mHSPC.[28, 29, 55] In the pivotal trial for apalutamide, named TITAN, apalutamide + ADT vs placebo + ADT reduced the risk of radiographic progression free survival or death by 52% (HR, 0.48; p<0.001) and increased overall survival by 33% (HR, 0.67; p=0.005).[55] However, a recent report on treatment of mHSPC in England suggests there is significant underuse of treatment intensification, especially among those who are older, frail and/or from economically deprived areas.[52]

This submission considers darolutamide + ADT for the treatment of chemotherapy (i.e. docetaxel) ineligible patients with mHSPC. This treatment option would be an alternative first-line treatment to apalutamide + ADT, which has been recommended by NICE TA741 specifically as a treatment for patients with mHSPC ineligible for docetaxel.[56] Apalutamide is therefore the key comparator to darolutamide in this submission. As well being recommended by NICE in an identical position in the treatment pathway, apalutamide is from the same drug class as darolutamide and has the same mode of action and administration. This approach has been validated by UK clinicians.[22, 23]

Patients who are not suitable for docetaxel treatment are identified by their clinicians on a case-by-case basis, using a clinical framework of risk based on contraindications (factors that would make the treatment harmful to the patient) listed in the docetaxel summary of product characteristics (SmPC), those with overall poor performance status (defined by clinical criteria established by WHO or the Eastern Cooperative Oncology Group [ECOG]), and/or those with significant co-existing conditions.[56, 57] Patients who choose not to have docetaxel are also considered docetaxel ineligible.[56]

Men with mHSPC need access to prostate cancer therapies with fewer treatment-related toxicities because treatment toxicity is one of the main reasons they are not able to receive more effective intensified treatment regimens, meaning they are likely to progress to mCRPC more quickly and have poorer survival. Darolutamide + ADT has a favourable tolerability and when compared with

enzalutamide and apalutamide, based on evidence from three pivotal darolutamide prostate cancer trials: ARASENS,[17, 58] ARAMIS[59] and ARANOTE.[60]

In ARANOTE, which provides the key evidence for this submission, adverse events (AEs) commonly associated with ARTA treatment (known as Treatment-Emergent Adverse Events or TEAEs), were generally similar to placebo for darolutamide, and there were low rates of AEs that affect patients' daily living activities (ADL).[60] In comparison, apalutamide[55] and enzalutamide[28] are associated with burdensome treatment-related toxicities, particularly fatigue and rash (in the case of apalutamide). Fatigue not only impacts the physical well-being of patients but also affects their mental health and quality of life. In younger patients, it affects their ability to work and often leads to a reduction or delay in treatment and dosages use in older patients. Expert clinicians confirm fatigue is an important factor influencing the use of treatment intensification in patients in England and Wales.[22, 23, 61]

As well as fatigue, enzalutamide use is associated with mental impairment,[28, 61] and both apalutamide and enzalutamide were associated with severe (Grade 3) seizures in clinical trials.[28, 55, 61] Darolutamide shows no increased signal for mental impairment, and patients with a history of epileptic seizures are permitted to use darolutamide, which represents a small but significant population who have not been able to receive ARTA doublet therapy.[60, 61] Low central-nervous system side effects seen with darolutamide compared with apalutamide and enzalutamide are related to its different chemical structure, which results in less non-specific binding to other receptors[61-64] and low penetration of the brain.[61]

Dermatologic toxicities and hypothyroidism are a significant concern with apalutamide.[23, 55] Skin rashes, and alterations in nail and health and hair due to apalutamide affect physical appearance and lead to considerable emotional distress.[61, 65] Dermatologic and thyroid toxicities also have a significant impact on patients and healthcare resource use.[22, 23] In the case of rash, there is a need for increased visits to healthcare providers, dermatologic consultations, additional medications to treat symptoms, as well as dose interruptions and discontinuation of mHSPC treatment,[22] whilst the requirement for thyroid function tests adds an additional level of monitoring and complexity to patients being treated with apalutamide.[23] Whilst dermatologic and thyroid toxicities are prevalent for apalutamide in TITAN,[55] data from ARANOTE suggests darolutamide has no increased signal for rash, and a lower than placebo effect on thyroid function.[66]

Preventing progression to mCRPC is a key treatment goal of mHCPC therapy and patients experiencing treatment-related toxicities, are more likely to discontinue drug treatment and have poorer overall outcomes. Clinical studies show more patients on apalutamide[55, 67] and enzalutamide[28] than placebo discontinue treatment,[60] whilst ARANOTE is the only study in mHSPC to show lower discontinuation rates due to AEs in the treatment arm vs placebo (6.1% vs 9.0%), meaning patients stay on beneficial treatment for longer.[60] Lower levels of treatment discontinuation for darolutamide compared with apalutamide were confirmed using a statistical analysis technique called an indirect treatment comparison (ITC), which allows a comparison between treatments that were not compared in the same study.

The risk of interactions with other medications is a significant concern with use of apalutamide and enzalutamide. These interactions are a particular concern in patients with mHSPC, as patients are typically elderly and taking multiple medications (polypharmacy).[68-73] The British National Formulary (BNF) lists 310 potential drug interactions for apalutamide, and fewer than 45 for darolutamide (accessed April 2025).[33, 34, 74] A significant collaborative effort is needed among GPs, prescribing pharmacists, and oncologists to avoid DDIs and ensure safe and effective medication management in patients with mHSPC.[22] It is a key issue that apalutamide and enzalutamide

interact with a number of agents used to treat some of the most common conditions found in patients with mHSPC, such as cardiovascular disease.[75-77] Clinicians in England and Wales report a need to switch medications in 10–50% of patients, especially among those receiving cardiovascular agents, whilst hospital pharmacists do not prescribe apalutamide to patients with mHSPC and atrial fibrillation due to risks of DDIs.[22] Of particular concern is apalutamide's interaction with the new oral ADT therapy relugolix. ARTA therapy needs to be administered in combination with ADT, and manufacturer's guidance states that use of relugolix with apalutamide is not recommended,[78] while the BNF says apalutamide use is to be avoided with relugolix.[79]

The reimbursement by NICE of darolutamide + ADT is expected by clinicians to help to address many unmet needs in patients with mHSPC. Expert opinion from the Advanced Prostate Cancer Consensus Conference (APCCC) in 2024 confirmed darolutamide as a better tolerated treatment option than apalutamide or enzalutamide in patients with advanced cancer, with pre-existing diseases, and for older patients.[80] Clinicians in England and Wales confirm that darolutamide's improved tolerability and low potential for interactions with other medications may simplify treatment management and allow treatment intensification in patients with comorbidities and who are taking multiple medications that make them ineligible for currently available treatments.[22]

2d) Patient-based evidence (PBE) about living with the condition

International guidelines, clinical societies, and an international Delphi panel agree holistic assessment should form the foundation of high-quality care in prostate cancer.[81-83] Patient values and preferences are key to treatment decisions for mHSPC.[20, 51] In a study looking at patient preferences that included a group of patients from the UK, patients had a strong preference for effective treatments that improve survival and which avoid treatment-related side effects.[20, 84-87] There was a particularly strong desire in patients to avoid rash at all levels of severity, which is one of the most concerning side effects related to apalutamide use.[76, 77, 86] There is a clear unmet need in England for a new medication to treat mHSPC with fewer side effects.

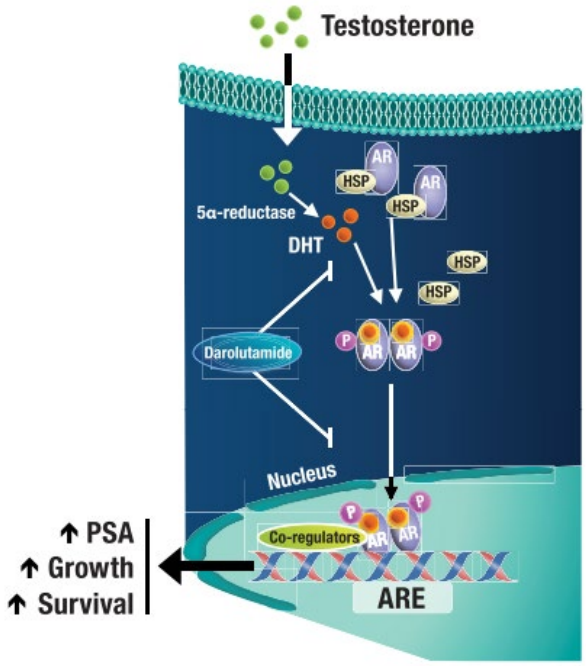
SECTION 3: The treatment

3a) How does the new treatment work?

The development, growth, and survival of prostate cells, both normal and cancerous, depends on androgens (e.g., testosterone) and the androgen receptor (AR) pathway.[88] The AR pathway is therefore a key target for drugs used in the treatment of prostate cancer.[45]

Darolutamide is an AR inhibitor (also known as an 'ARTA') with powerful anti-cancer activity. It works similarly to apalutamide to inhibit androgen binding, the transport of ARs across the nuclear membrane of a cell (known as nuclear translocation), and AR mediated transcription – processes that are critical to prostate cancer cell growth and differentiation.[62, 89] However, the chemical structure of darolutamide is distinct from apalutamide and enzalutamide. This means it has less capacity to cross the blood brain barrier than apalutamide and enzalutamide and potential for fewer and less severe toxic CNS-related side effects.[62-64]

Figure 1: Mechanism of action of darolutamide



Key: AR, androgen receptor; ARE, androgen-response element; DHT, dihydrotestosterone; HSP, heat shock protein; P, phosphate; PSA, prostate-specific antigen.

Source: Fizazi et al. 2018.[90]

3b) Combinations with other medicines

Darolutamide is to be used in combination with ADT. ADT (through surgical or medical means), targets the AR signalling pathway and aims to achieve castration levels of testosterone, critical to prostate cancer cell growth and differentiation (see Figure 1 Section 3a).[45] However, combining ADT with an ARTA, such as darolutamide, is a more effective treatment approach because this combination works together using complementary mechanisms to optimise the blockade of the AR pathway essential to prostate cancer growth and so enhance the beneficial effects on prostate tumours.[45, 46]

The side effects of ADT may include the following:

- Bone thinning (osteoporosis) which can increase risk of fractures
- Erectile dysfunction (difficulty in maintaining an erection
- Fatigue (persistent tiredness and lack of energy)
- Growth of breast tissue leading to enlargement of the breasts, known as gynecomastia
- Heart disease
- Hot flashes (sudden occurrences of flushing and/or sweats)
- Loss of sex drive
- Loss of muscle tissue, leading to a decrease in muscle strength and size
- Weight gain, due to increased body fat
- Dementia and Alzheimer's disease[91]

3c) Administration and dosing

Darolutamide is for oral use. The recommended dose of darolutamide is 600 mg (two 300 mg film-coated tablets), twice daily, equivalent to a total daily dose of 1200 mg. Tablets should be

swallowed whole and taken with food. Patients should continue to receive ADT with an LHRH agonist or antagonist GnRH analogue (if not surgically castrated) during darolutamide treatment of patients. Treatment of darolutamide should be continued until the disease progresses or until unacceptable toxicity occurs.

The method of administration for darolutamide is similar to apalutamide. The recommended dose for apalutamide is 240 mg as an oral single daily dose.

3d) Current clinical trials

The ARANOTE phase III trial is the key clinical trial investigating the effectiveness and safety of darolutamide + ADT compared with placebo (an inactive substance) + ADT in patients with mHSPC. The study was a global clinical trial conducted in 15 countries across 133 sites in Europe, Asia, Australia, Canada, South Africa, and Latin America.

The study enrolled a population of patients that was representative of the diversity of patients with mHSPC in the real-world and the UK. Briefly, patients were eligible to join the study if they were 18 years of age or older, had an ECOG performance status of 0–2, and had adequate bone marrow, liver, and renal functioning. The study included patients with newly diagnosed and recurrent mHSPC. In contrast to mHSPC trials for apalutamide and enzalutamide, patients with a history of seizures were also allowed to participate in the study. Patients showing metastases in regional lymph nodes only or with a scan at the start of the study showing high levels of metastatic disease in the bones were excluded from trial participation. Patients who had been treated with ARTAs, abiraterone, chemotherapy for prostate cancer, or radiotherapy in the 2 weeks prior to beginning the study were also prevented from joining the trial.[60, 66]

A total of 669 patients were enrolled in the study. All patients were on or began ADT within 12 weeks of starting darolutamide or placebo. A total of 446 patients received darolutamide 600 mg twice daily, while 223 patients were given a placebo twice daily. To prevent bias, study participants and personnel conducting and investigating the study did not know which patients received darolutamide, and which received placebo. All patients received either darolutamide or placebo until disease progression, unacceptable toxicity, and/or starting a new anticancer therapy, based on patient or physician decision, or interruption of study drug for more than 28 days in a row.[60, 66]

During the treatment phase of the study and for one year afterwards, patients were evaluated at clinic visits every 12 weeks. Participants then entered a long-term (survival) follow-up period where they were contacted by telephone approximately every 12 weeks.

To determine whether darolutamide + ADT improved patient outcomes in mHSPC, several measurements known as study endpoints were evaluated. The most important endpoint, the 'primary endpoint', was radiographic progression-free survival (rPFS). This was defined as the time from when patients were allocated to a treatment group (known as randomisation) to the first imaging-based documentation of progressive disease or death.[36, 66, 92]

PFS is often used as the key clinical effectiveness outcome in cancer clinical trials because it is directly related to overall survival (OS) but can be determined much quicker than OS, meaning trials can complete sooner giving patients quicker access to beneficial treatments.

Secondary endpoints were:

- OS – measures how long a person lives from the start of the trial until death
- Time to initiation of a subsequent systemic anticancer therapy for prostate cancer
- Time to CRPC – defined as time from randomisation to PSA or radiological progression
- Time to PSA progression – defined as time from the start of the trial until levels of PSA increase
- PSA undetectable rate – defined as the percentage with detectable PSA values that became undetectable
- Time to pain progression – defined as the length of time that passes between starting the from the until pain worsens

Adverse events were assessed from the first dose of study drug until 30 days after the last treatment. An independent data monitoring committee reviewed safety data throughout the study.[60, 66]

The ARANOTE study was initiated on 23 February 2021 and had a primary completion date of 7 June 2024. Final OS analysis was obtained on 10 January 2025 but is still considered confidential therefore not included within this document. Therefore, the efficacy data and safety data presented in this submission are from the primary completion analysis.[60]

3e) Efficacy

Data from the ARANOTE study primary completion analysis showed darolutamide + ADT demonstrated significant and clinically meaningful improvements in rPFS compared with placebo + ADT (Table 1). Darolutamide + ADT significantly reduced the risk of rPFS or death by 46%. At 2 years of follow-up, rPFS was 70.3% for patients taking darolutamide and 52.1% for those on placebo.

The primary completion analysis data suggests there is an overall survival benefit for darolutamide, but the results were not statistically significant. This suggestive benefit was seen even though the ARANOTE study was not specifically designed to look for an improvement in OS. Darolutamide has already been shown to improve OS in the same patient population in the ARASENS study (which assessed the beneficial clinical effect of darolutamide + ADT + docetaxel)[58] and in combination with ADT in patients with nmCRPC in the ARAMIS study.[59] ARANOTE data builds upon convincing clinical evidence already established in ARASENS and ARAMIS showing that its use improves survival.[58, 59] Clinicians in England and Wales have confirmed they would be confident to prescribe darolutamide, based on this collective body of evidence.[22, 23]

In terms of the other clinical endpoints, a beneficial effect of darolutamide compared with placebo was observed in all other clinical outcomes assessed in ARANOTE.[60] Darolutamide + ADT delayed progression to end-stage disease mCRPC. Patients on darolutamide did not reach a median time to progression, whilst those on placebo progressed to CRPC with a median time of 13.8 months.[60] A lower percentage of patients progressed to mCRPC when on darolutamide (34.5%), compared to placebo (60%).[60] Similarly, patients on darolutamide did not reach a median time to PSA progression on darolutamide but reached PSA progression at a median time of 16.8 months when on placebo. A higher proportion of patients on darolutamide than placebo reached

an undetectable PSA rate (62.6% vs 18.5%).[60] These results reflect similar deep and durable PSA responses seen in the ARASENS study.[66]

Table 1: Key efficacy outcomes reported in ARANOTE

	Darolutamide + ADT (n=446)		Placebo + ADT (n=223)		
	Median, months	**Events, No (%)**	**Median, months**	**Events, No.**	**HR[a] (95% CI; p value)**
Primary endpoint					
rPFS	NR	128 (28.7)	25.0	94 (42.2)	0.54 (0.41–0.71; p<0.0001)
Secondary endpoints					
OS	NR	103 (23.1)	NR	60 (26.9)	0.81 (0.59–1.12)
Time to CRPC	NR	154 (34.5)	13.8	143 (64.1)	0.40 (0.32–0.51)
Time to PSA progression	NR	93 (20.9)	16.8	108 (48.4)	0.31 (0.23–0.41)
Time to initiation of subsequent systemic anticancer therapy	NR	68 (15.2)	NR	74 (33.2)	0.40 (0.29–0.56)
Time to pain progression (BPI-SF)	NR	124 (27.8)	29.9	79 (35.4)	0.72 (0.54–0.9)
PSA rates					
Detectable PSA values ≥0.2 ng/ml at baseline, N (%)[b] [95% CI]	425 (100.0)		211 (100.0)		
PSA undetectable rates (<0.2 ng/mL), n (%) [95% CI]	266 (62.6) [57.8–67.2]		39 (18.5) [13.5–24.4]		Rate difference[c]: 44.3 (37.4–51.2)

The primary endpoint rPFS and all secondary endpoints (other than OS) are from the primary completion analysis DCO Jun 7, 2024

[a]Hazard ratio and 95% CI are based on Cox regression model, stratified by visceral disease (present vs absent) and prior local therapy (yes vs no). [b]Percentages are based on participants who had a detectable PSA value at baseline. [c]The rate difference and 95% CI were based on a Cochran-Mantel-Haenszel test comparing between the treatment arms, stratified by IWRS stratification factors: visceral metastases (present vs. absent) and prior local therapy (yes vs. no).

Abbreviations: ADT: androgen-deprivation therapy; BPI-SF: Brief Pain Inventory: Short Form; CI: confidence interval; HR: hazard ratio; mCRPC: castration-resistant prostate cancer; NA: not applicable; NR: not reached; OS: overall survival; rPFS: radiological progression-free survival PSA: prostate-specific antigen.

Source: ARANOTE Clinical Study Report September 2024, Bayer AG[66]; Saad *et al.* 2024[60]

A limitation of the evidence base is that there are no clinical trials which directly compare the efficacy of darolutamide + ADT with apalutamide + ADT, the comparator for this cost-comparison appraisal. To address this, a statistical method called an indirect treatment comparison was used to compare these treatments. Results from the ITC suggested there is no difference between darolutamide + ADT and apalutamide + ADT in terms of their effectiveness in prolonging rPFS and OS. Expert clinicians stated these results are as expected because both drugs are in the same class of treatments.[23]

Other limitations of the ARANOTE study include use of placebo + ADT as the comparator, as ADT monotherapy is no longer a standard of care; however, a significant number of patients still receive ADT monotherapy in England and Wales, so this is still a relevant comparator for clinicians making treatment decisions. Finally, the ARANOTE study was not designed to detect differences in OS because OS has already been shown for darolutamide in patients with mHSPC in ARASENS[58] and in patients with mCRPC in ARAMIS.[59] The strengths of the trial include that the patients who

participated in the trial represented the diverse patient population needing treatment in the UK, including the elderly and patients from different ethnic backgrounds. Overall, data from the ARANOTE trial adds to the existing evidence that supports darolutamide's effectiveness and safety in mHSPC.[59, 60, 90]

3f) Quality of life impact of the medicine and patient preference information

Quality of life benefits in the ARANOTE study were measured using the Brief Pain Inventory – Short Form (BPI-SF) questionnaire. This questionnaire is one of the most widely used measurements for assessing clinical pain and was developed specifically to assess pain related to cancer.[93] Briefly the BPI-SF is a nine-item questionnaire where individuals rate the severity of their pain and the impact it has on their ability to go about their daily life using a 0–10 scale.[93] The BPI measures how much pain has interfered with seven daily activities, including general activity, walking, work, mood, enjoyment of life, relationships with others, and sleep.[93]

BPI-SF results reported in ARANOTE showed darolutamide treatment improved patient quality of life. A lower percentage of patients taking darolutamide compared with placebo had pain progression (27.8% vs 35.4%). Darolutamide also delayed the time to pain progression and/or the initiation of opioid use. The median time to pain progression was not reached in patients taking darolutamide compared to 29.9 months in those on placebo.[66] At 2 years, a higher proportion of patients on darolutamide than placebo were event-free without pain progression (68.0% vs 58.5%).[66]

Results from an indirect treatment comparison looking at patient-reported outcomes of time to deterioration (Functional Assessment of Cancer Therapy – Prostate; FACT-P scores) showed there was strong evidence of a shorter time until deterioration in scores for patients on apalutamide + ADT vs darolutamide + ADT, which could mean patient quality of life is better when receiving darolutamide + ADT compared with apalutamide + ADT.

3g) Safety of the medicine and side effects

The safety of the treatments used in ARANOTE were monitored by recording any unexpected AEs that the patients in the study experienced which may or may not be related to the study treatments.

Safety results from ARANOTE confirmed darolutamide's favourable tolerability as seen in the other prostate cancer trials using darolutamide, namely ARAMIS and ARASENS trials.[58, 60, 94] In fact, ARANOTE is the first and only study of an ARTA in prostate cancer to show safety outcomes that are similar to the inactive placebo agent.[28, 55, 60, 61]

In summary:

- Rates of the most common AEs occurring in ≥5% of patients with darolutamide + ADT were low, mostly Grade 1 or Grade 2 events, and similar to placebo + ADT.
- Similar and low rates of TEAEs (Any, Serious and Grade 3 or 4) for darolutamide + ADT vs placebo + ADT were also found.

There were also low incidences of AEs associated with other ARTAs:

- Similar rates of hypertension were reported for darolutamide and placebo (9.4% vs 9.5%).

- Darolutamide-treated patients had a lower rate of fatigue vs placebo (5.6% vs 8.1%).
- A low percentage of darolutamide-treated patients had rash (4.3% vs 3.6% for darolutamide vs placebo).[60]
- No patients had a seizure in ARANOTE.

The rate of adverse events was analysed to take into account the length of time patients were treated either with darolutamide + ADT or placebo ADT (known as the exposure-adjusted incidence rate; EAIR). These results in the table below show that the rate of AEs is similar in both treatment arms.

Table 2: TEAE exposure-adjusted incidence rates (EAIR)

Adverse Events Commonly Associated With ARPI	Darolutamide + ADT (N=445)	Placebo + ADT (N=221)
	EAIR[b]/100 PY	EAIR[b]/100 PY
Hypertension	5.5	6.7
Vasodilatation and flushing	5.6	5
Diabetes mellitus and hyperglycemia	5.3	6.7
Cardiac arrhythmias	5.1	4.7
Fatigue	3.2	5.7
Rash	2.4	2.4
Bone fracture	2.3	1.5
Coronary artery disorders	2	0.9
Decreased weight	1.8	1.8
Mental-impairment disorder	0.9	0.3
Falls, including accident	0.8	0.6
Heart failure	0.5	0.6
Depressed-mood disorder	0.2	0.6
Cerebral ischemia	0.1	0.9

Abbreviations: ADT, androgen-deprivation therapy; ARPI, androgen receptor pathway inhibitor; EAIR, exposure-adjusted incidence rate; MedDRA, Medical Dictionary for Regulatory Activities; PY, patient years.

Source: Saad *et al.* 2024.[60]

ARANOTE is the only ARTA study in pivotal prostate cancer clinical trials where fewer patients discontinued therapy due to AEs in the treatment arm vs the placebo arm (6.1% vs 9.0%).[60] This is an important finding as it means patients are likely to stay on beneficial treatment for longer.

As stated above, there are no clinical trials which directly compare the safety profiles of darolutamide and apalutamide, the comparator for this appraisal. To address the lack of data an indirect treatment comparison was carried out comparing published results from TITAN[55] with ARANOTE[60] data. The results of the analyses demonstrated that patients treated with apalutamide + ADT vs darolutamide + ADT or placebo + ADT were at higher risk of Grade 3–5 AEs. The results also confirm that there was a higher risk of treatment discontinuation due to an AE for patients treated with apalutamide + ADT vs darolutamide + ADT or placebo + ADT. The results of the analyses were shared with UK clinicians, and clinicians agree that the key difference between darolutamide and apalutamide is the beneficial safety profile of darolutamide and that this should be considered in NICE decision making.[23]

3h) Summary of key benefits of treatment for patients

- Darolutamide + ADT doublet therapy is being submitted to NICE for the treatment of adult men with mHSPC who are ineligible for docetaxel therapy.
- Darolutamide + ADT addresses a key unmet need in patients who have characteristics or co-existing long-term conditions that make them unable to receive optimal intensified treatment with darolutamide + ADT + docetaxel or currently available ARTA (apalutamide or enzalutamide) + ADT doublet therapies.
- In the ARANOTE study of patients with mHSPC, darolutamide + ADT significantly improved progression free survival by 46%. Improvement in OS was also suggested, although these data are not yet final and the study was not designed to look at overall survival.[60]
- Darolutamide + ADT improved all other important endpoints tested in the ARANOTE study, including the time it took patients to progress to mCRPC, the time to worsening of pain, and reduced the overall number of patients who progressed to mCRPC or whose pain worsened.
- Other improvements shown with darolutamide were high numbers of patients still having undetectable PSA levels (62.6% vs 18.5% for placebo), and a ~70% reduction in the time until patient PSA levels began to increase. Darolutamide + ADT also delayed the time until patients needed to take another anti-cancer treatment.
- Results from ARANOTE suggest darolutamide + ADT improves patient quality of life. In addition to improvements in BPI-SF score, indirect treatment comparison data indicates strong evidence that there is a longer time until patient deterioration for patients taking darolutamide + ADT compared with apalutamide + ADT.
- Results from an indirect treatment comparison show that while darolutamide + ADT has the same mechanism of action as apalutamide + ADT, and a similar effectiveness in prolonging survival, its use lead to significantly fewer people withdrawing from treatment due to side effects from the treatment.
- The ARANOTE study, which looks at the safety and effectiveness of darolutamide + ADT in patients with mHSPC, is the first and only study of an ARTA in prostate cancer to show placebo-like safety.[28, 55, 60, 61]
- Using darolutamide + ADT means that patients with mHSPC may be able to stay on intensified treatment for longer and see more benefit because ARANOTE is the only clinical trial in mHSPC to show fewer patients stopping active treatment vs placebo due to side effects.[28, 55, 60]
- Darolutamide in ARANOTE has a low level of CNS side effects when compared with apalutamide, likely related to its distinct chemical structure that prevents it from passing so easily through the blood brain barrier.[63, 95, 96]
- Safety data for darolutamide from ARANOTE shows there was no increased risk in certain concerning side effects found with apalutamide, including rash, fatigue and thyroid issues.[55, 60, 61] Of significant interest is the finding that patients treated with darolutamide in ARANOTE had a lower rate of fatigue than those treated with placebo (5.6% vs 8.1%).[60]
- Patients on darolutamide are less likely to be at risk of a potential drug interaction than those taking apalutamide or enzalutamide. The BNF reports fewer than 45 potential interactions for darolutamide,[74] whilst apalutamide and enzalutamide interact with as many as 310 and 233 medications, respectively,[33, 34] including those used to treat conditions commonly found in patients with mHSPC, such as cardiovascular disease.[33, 34]
- Darolutamide treatment is easier to manage than other ARTAs because its low level of side effects and drug interactions mean there's less need for additional monitoring tests (e.g., for thyroid disease) or visits to healthcare providers.[22, 23]

3i) Summary of key disadvantages of treatment for patients

The effectiveness of darolutamide is similar to apalutamide. Importantly, the ARANOTE study is the first and only study of an ARTA to show placebo-like safety outcomes,[28, 55, 60, 61] thus Bayer does not consider darolutamide to have any disadvantages compared to apalutamide in the first-line treatment of patients with mHSPC ineligible for docetaxel treatment.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

As noted above an analysis called an indirect treatment comparison suggested there is no difference between darolutamide + ADT and apalutamide + ADT in terms of their effectiveness in prolonging rPFS and OS, therefore no difference in effectiveness between these two treatments has been assumed. Therefore, a cost-comparison analysis has been conducted, to keep the analysis simple, it was also conservatively assumed that there was no difference in safety between darolutamide + ADT and apalutamide + ADT.

The cost-comparison analysis only considers the costs associated with treatment darolutamide + ADT versus treatment with apalutamide + ADT. Darolutamide and apalutamide are both oral medications, so there are no differences included in the resources needed to administer each drug. In terms of drug monitoring and resource utilisation, it was highlighted by UK clinicians that these would be somewhat reduced for patients treated with darolutamide compared to apalutamide, as there would be a reduced need for changes to other medications with potential interactions with darolutamide compared to apalutamide. Additionally, no testing for thyroid function is needed for patients treated with darolutamide, which is a requirement for patients treated with apalutamide.
While the reduced resource utilisation and reduced adverse events may lead to reduced overall costs, the cost-comparison analysis conservatively assumed there was no difference in any costs except the acquisition costs of darolutamide and apalutamide.

The outcome of the cost-comparison analysis showed that darolutamide + ADT generates cost savings per patient compared with apalutamide + ADT, when the discounted price for darolutamide is considered.

The main uncertainty in the cost-comparison analysis comes from the time on treatment with darolutamide + ADT versus apalutamide + ADT. The analysis assumes no difference between the treatments with regards to this, but the method used to extrapolate the duration of treatment observed in the ARANOTE trial to later years, has a relatively high impact on outcomes of that analysis. Therefore, additional analyses were performed to test alternative extrapolation methods as well as a reduced time horizon of the analysis. These analyses increased the difference in total costs between darolutamide + ADT and apalutamide + ADT.

3j) Innovation

Darolutamide has a similar mechanism of action to apalutamide and enzalutamide which are both used in England to treat mHSPC. However, darolutamide was specifically designed with unique structure. This means that although it is at least as effective at treating mHSPC as apalutamide, it has fewer side effects than apalutamide and enzalutamide, and less potential for drug interactions.

The availability of darolutamide will address a current key unmet need in patients who are unable to receive optimal therapy with an ARTA + ADT due to the potential for side effects and treatment interactions, such as the elderly, those with cognitive impairments or potential to suffer from seizures, or with co-existing conditions that may mean they are more likely to have a drug interaction.

3k) Equalities

Patients with mHSPC are affected by healthcare and access inequalities. Some ethnic groups have higher incidences of prostate cancer, such as Black males and data suggests this patient population is also affected by healthcare inequalities as the mortality rate for Black males is approximately 2.1 times higher than White males.[4, 97-99] The National Prostate Cancer Audit (NCPA) has highlighted the need for more equitable access to newer prostate cancer therapies across the UK.[2]

The currently available ARTA treatment options for mHSPC, such as apalutamide, are not recommended for patients with a history of seizures, and these patients were excluded from the pivotal trials.[28, 55] In clinical practice, the only treatment option for these patients is ADT monotherapy which is not as effective. This exclusion highlights a small but significant equality gap in the treatment pathway, leaving an underrepresented group of patients with suboptimal treatment options.

SECTION 4: Further information, glossary and references

4a) Further information

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Response:

Where appropriate, terminology has been explained within the body of the document.

4c) References

Response:
1. It's a fact: prostate cancer now England's most common cancer. [press release]. PCUK, 28 January 2025 2025.
2. NPCA. National Prostate Cancer Audit Quality Improvement Plan – September 2024. 2024.
3. Prostate Cancer UK: Prostate cancer statistics 2023 [updated August 2023. Available from: https://prostatecanceruk.org/for-health-professionals/data-and-evidence.
4. National Cancer Institute (NCI). Cancer stat facts: Prostate cancer 2023 [Available from: https://seer.cancer.gov/statfacts/html/prost.html.
5. Parker C, Castro E, Fizazi K, Heidenreich A, Ost P, Procopio G, et al. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020;31(9):1119-34.
6. Cancer Research UK: Prostate cancer statistics [Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer#heading-Zero
7. National Prostate Cancer Audit (NPCA). Patient Summary of NPCA 2024 State of the Nation. 2024.
8. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024;74(1):12-49.
9. Desai MM, Cacciamani GE, Gill K, Zhang J, Liu L, Abreu A, et al. Trends in Incidence of Metastatic Prostate Cancer in the US. JAMA Netw Open. 2022;5(3):e222246.
10. National Prostate Cancer Audit (NPCA). NPCA Annual Report 2020 (updated: January 2021) 2021 [Available from: https://www.npca.org.uk/reports/npca-annual-report-2020/.

11. National Prostate Cancer Audit (NPCA). NPCA Annual Report 2021 (updated: January 2022) 2022 [Available from: https://www.npca.org.uk/reports/npca-annual-report-2020/.
12. Agarwal N, McQuarrie K, Bjartell A, Chowdhury S, Pereira de Santana Gomes AJ, Chung BH, et al. Health-related quality of life after apalutamide treatment in patients with metastatic castration-sensitive prostate cancer (TITAN): a randomised, placebo-controlled, phase 3 study. Lancet Oncol. 2019;20(11):1518-30.
13. Stenzl A, Dunshee C, De Giorgi U, Alekseev B, Iguchi T, Szmulewitz RZ, et al. Effect of Enzalutamide plus Androgen Deprivation Therapy on Health-related Quality of Life in Patients with Metastatic Hormone-sensitive Prostate Cancer: An Analysis of the ARCHES Randomised, Placebo-controlled, Phase 3 Study. Eur Urol. 2020;78(4):603-14.
14. Chi KN, Protheroe A, Rodriguez-Antolin A, Facchini G, Suttman H, Matsubara N, et al. Patient-reported outcomes following abiraterone acetate plus prednisone added to androgen deprivation therapy in patients with newly diagnosed metastatic castration-naive prostate cancer (LATITUDE): an international, randomised phase 3 trial. Lancet Oncol. 2018;19(2):194-206.
15. Morgans AK, Chen YH, Sweeney CJ, Jarrard DF, Plimack ER, Gartrell BA, et al. Quality of Life During Treatment With Chemohormonal Therapy: Analysis of E3805 Chemohormonal Androgen Ablation Randomized Trial in Prostate Cancer. J Clin Oncol. 2018;36(11):1088-95.
16. Rush HL, Murphy L, Morgans AK, Clarke NW, Cook AD, Attard G, et al. Quality of Life in Men With Prostate Cancer Randomly Allocated to Receive Docetaxel or Abiraterone in the STAMPEDE Trial. J Clin Oncol. 2022;40(8):825-36.
17. Fizazi K, Smith MR, Hussan M, et al. Quality of life and patient-relevant endpoints with darolutamide in the phase 3 ARASENS study. ESMO Congress 2022; September 9-13, 2022; Paris, France2022.
18. Drudge-Coates L, Oh WK, Tombal B, Delacruz A, Tomlinson B, Ripley AV, et al. Recognizing Symptom Burden in Advanced Prostate Cancer: A Global Patient and Caregiver Survey. Clin Genitourin Cancer. 2018;16(2):e411-e9.
19. Kretschmer A, van den Bergh RCN, Martini A, Marra G, Valerio M, Tsaur I, et al. Assessment of Health-Related Quality of Life in Patients with Advanced Prostate Cancer-Current State and Future Perspectives. Cancers (Basel). 2021;14(1).
20. Connor MJ, Genie MG, Burns D, Bass EJ, Gonzalez M, Sarwar N, et al. A Systematic Review of Patients' Values, Preferences, and Expectations for the Treatment of Metastatic Prostate Cancer. Eur Urol Open Sci. 2022;36:9-18.
21. Hall F, de Freitas HM, Kerr C, Ito T, Nafees B, Lloyd AJ, et al. Estimating utilities/disutilities for high-risk metastatic hormone-sensitive prostate cancer (mHSPC) and treatment-related adverse events. Qual Life Res. 2019;28(5):1191-9.
22. Bayer AG. ARANOTE Advisory Board Meeting: Understanding the future metastatic hormone sensitive prostate cancer (mHSPC) landscape. Bayer AG; 2024 6 December 2024.
23. Bayer AG. NICE Advisory Board Meeting: Darolutamide in combinatino with ADT for the treatment of metastatic hormone sensitive prostate cancer. 11 Februrary 2025.; 2025.
24. James C, Brunckhorst O, Eymech O, Stewart R, Dasgupta P, Ahmed K. Fear of cancer recurrence and PSA anxiety in patients with prostate cancer: a systematic review. Support Care Cancer. 2022;30(7):5577-89.
25. Prostate Cancer UK. Fatigue and prostate cancer factsheet.
26. Grunfeld EA, Drudge-Coates L, Rixon L, Eaton E, Cooper AF. "The only way I know how to live is to work": a qualitative study of work following treatment for prostate cancer. Health Psychol. 2013;32(1):75-82.
27. Cornford P, Tilki D, van den Bergh RCN, Eberli D, De Meerleer G, De Santis M, et al. EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on Prostate Cancer. Arnhem, The Netherlands: EAU Guidelines Office; 2025.

28. Armstrong AJ, Szmulewitz RZ, Petrylak DP, Holzbeierlein J, Villers A, Azad A, et al. ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men With Metastatic Hormone-Sensitive Prostate Cancer. J Clin Oncol. 2019;37(32):2974-86.
29. Chi KN, Chowdhury S, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, et al. Apalutamide in Patients With Metastatic Castration-Sensitive Prostate Cancer: Final Survival Analysis of the Randomized, Double-Blind, Phase III TITAN Study. J Clin Oncol. 2021;39(20):2294-303.
30. Goebell PJ, Raina R, Chen S, Rege S, Shah R, Grossman JP, et al. Real-world treatment of metastatic hormone-sensitive prostate cancer in the USA, Europe and Asia. Future Oncol. 2024.
31. Lu-Yao G, Nightingale G, Nikita N, Keith S, Gandhi K, Swartz K, et al. Relationship between polypharmacy and inpatient hospitalization among older adults with cancer treated with intravenous chemotherapy. Journal of Geriatric Oncology. 2020;11(4):579-85.
32. Appukkuttan S, Ko G, Fu C, Bannister B, Kong SX, Jhaveri J, et al. Drug–drug interaction potential among patients with nonmetastatic castration-resistant prostate cancer (nmCRPC) treated with novel androgen receptor inhibitors. Expert Review of Anticancer Therapy.1-9.
33. BNF. British National Formulary: Apalutamide drug interactions 2025 [Available from: https://bnf.nice.org.uk/interactions/apalutamide/.
34. BNF. British National Formulary: Enzalutamide drug interactions 2025 [Available from: https://bnf.nice.org.uk/interactions/enzalutamide/.
35. Boye M, Ribbands A, Leith A, Clayton E, Butcher J, Rybowski S. Real-world health-related quality of life and caregiver need in patients with metastatic hormone-sensitive and metastatic castration-resistant prostate cancer. Journal of Clinical Oncology. 2022;40(6_suppl):54-.
36. Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016;34(12):1402-18.
37. Scher HI, Solo K, Valant J, Todd MB, Mehra M. Prevalence of Prostate Cancer Clinical States and Mortality in the United States: Estimates Using a Dynamic Progression Model. PLoS One. 2015;10(10):e0139440.
38. Wenzel M, Preisser F, Hoeh B, Schroeder M, Würnschimmel C, Steuber T, et al. Impact of Time to Castration Resistance on Survival in Metastatic Hormone Sensitive Prostate Cancer Patients in the Era of Combination Therapies. Front Oncol. 2021;11:659135.
39. Appukkuttan S, Tangirala K, Babajanyan S, Wen L, Simmons S, Shore N. A Retrospective Claims Analysis of Advanced Prostate Cancer Costs and Resource Use. Pharmacoecon Open. 2020;4(3):439-47.
40. Hechmati G, Cure S, Gouépo A, Hoefeler H, Lorusso V, Lüftner D, et al. Cost of skeletal-related events in European patients with solid tumours and bone metastases: data from a prospective multinational observational study. J Med Econ. 2013;16(5):691-700.
41. Johanes C, Monoarfa RA, Ismail RI, Umbas R. Anxiety level of early- and late-stage prostate cancer patients. Prostate Int. 2013;1(4):177-82.
42. Saad F, Ivanescu C, Phung D, Loriot Y, Abhyankar S, Beer TM, et al. Skeletal-related events significantly impact health-related quality of life in metastatic castration-resistant prostate cancer: data from PREVAIL and AFFIRM trials. Prostate Cancer Prostatic Dis. 2017;20(1):110-6.
43. Office for National Statistics. Cancer survival in England - adults diagnosed (2013 - 2017 dataset). Updated: 12 August 2019 2019 [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed.
44. Rane JK, Chowdhury A, Kinnaird W. Treatment of metastatic hormone sensitive prostate cancer. Trends in Urol Men's Health. 2021;12:7-10.
45. Hamid AA, Sayegh N, Tombal B, Hussain M, Sweeney CJ, Graff JN, et al. Metastatic Hormone-Sensitive Prostate Cancer: Toward an Era of Adaptive and Personalized Treatment. Am Soc Clin Oncol Educ Book. 2023;43:e390166.

46. Thomas C, Baunacke M, Erb HHH, Fussel S, Erdmann K, Putz J, et al. Systemic Triple Therapy in Metastatic Hormone-Sensitive Prostate Cancer (mHSPC): Ready for Prime Time or Still to Be Explored? Cancers (Basel). 2021;14(1).
47. Cancer Research UK: Proportion of cancer cases by stage at diagnosis prostate cancer. Figures from 2018. 2024 [Available from: https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/.
48. Fizazi K, Gillessen S, clinicalguidelines@esmo.org EGCEa. Updated treatment recommendations for prostate cancer from the ESMO Clinical Practice Guideline considering treatment intensification and use of novel systemic agents. Ann Oncol. 2023;34(6):557-63.
49. NICE. NICE Guideline NG131: Prostate cancer: diagnosis and management. Published 9 May 2019. 2019 [updated 15 December 2021.
50. Kyriakopoulos CE, Chen YH, Carducci MA, Liu G, Jarrard DF, Hahn NM, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer: Long-Term Survival Analysis of the Randomized Phase III E3805 CHAARTED Trial. J Clin Oncol. 2018;36(11):1080-7.
51. Glen H, Bahl A, Clarke N, Jain S, Kalsi T, Khoo V, et al. A modified Delphi consensus regarding the clinical utility of triplet therapy in patients with metastatic hormone-sensitive prostate cancer patients in the UK (in press). 2024.
52. Dodkins J, Cook A, Mayne E, Parry M, Parry MG, Boyle J, et al. Are evidence-based guidelines translating into clinical practice? A national population-based study of the use of treatment intensification in metastatic hormone-sensitive prostate cancer (mHSPC) in England. Eur J Cancer. 2025;220:115335.
53. Docetaxel summary of product characteristics (SmPC). Sanofi-Aventis; December 2023.
54. Docetaxel prescribing information. Sanofi-Aventis; January 2023.
55. Chi KN, Agarwal N, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, et al. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med. 2019;381(1):13-24.
56. NICE. NICE Technology Appraisal TA741: Apalutamide with androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer – Technology appraisal guidance. October 28, 2021. 2021.
57. NHS England. Clinical Commissioning Policy Statement: Docetaxel in combination with androgen deprivation therapy for the treatment of hormone naïve metastatic prostate cancer (B15/PS/a). Updated: 20 January 2016. [Available from: https://www.england.nhs.uk/wp-content/uploads/2016/01/b15psa-docetaxel-policy-statement.pdf?UNLID=106952065020223157562 4.
58. Smith MR, Hussain M, Saad F, Fizazi K, Sternberg CN, Crawford ED, et al. Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer. N Engl J Med. 2022;386(12):1132-42.
59. Fizazi K, Shore N, Tammela TL, Ulys A, Vjaters E, Polyakov S, et al. Nonmetastatic, Castration-Resistant Prostate Cancer and Survival with Darolutamide. N Engl J Med. 2020;383(11):1040-9.
60. Saad F, Vjaters E, Shore M, Olmos D, Xing N, Pereira de Santana Gomes AJ, et al. Darolutamide in Combination With Androgen-Deprivation Therapy in Patients With Metastatic Hormone-Sensitive Prostate Cancer From the Phase III ARANOTE Trial. ESMO September 16, 2024. J Clin Oncol. 2024; 00:1-11.
61. Turco F, Di Prima L, Pisano C, Poletto S, De Filippis M, Crespi V, et al. How to Improve the Quality of Life of Patients with Prostate Cancer Treated with Hormone Therapy? Res Rep Urol. 2023;15:9-26.
62. Moilanen AM, Riikonen R, Oksala R, Ravanti L, Aho E, Wohlfahrt G, et al. Discovery of ODM-201, a new-generation androgen receptor inhibitor targeting resistance mechanisms to androgen signaling-directed prostate cancer therapies. Sci Rep. 2015;5:12007.

63. Zurth C, Sandman S, Trummel D, Seidel D, Nubbemeyer R, Gieschen H. Higher blood–brain barrier penetration of [14C]apalutamide and [14C]enzalutamide compared to [14C]darolutamide in rats using whole-body autoradiography. Genitourinary Cancers Symposium. Prostate Cancer-Advanced Disease. February 26, 2019. J Clin Oncol. 2019;37.
64. Crawford ED, Stanton W, Mandair D. Darolutamide: An Evidenced-Based Review of Its Efficacy and Safety in the Treatment of Prostate Cancer. Cancer Manag Res. 2020;12:5667-76.
65. Daher R, Ruplin A, Gupta S, Spiess PE, Kamat AM, Cigliola A, et al. The spectrum of cutaneous toxicities related to novel genitourinary cancer therapies. Crit Rev Oncol Hematol. 2024;200:104420.
66. Bayer. Clinical Study Report: Phase 3 study of darolutamide in addition to ADT versus placebo plus ADT in men with mHSPC (ARANOTE). 2024.
67. Smith MR, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN, et al. Apalutamide and Overall Survival in Prostate Cancer. Eur Urol. 2021;79(1):150-8.
68. Appukkuttan S, Ko G, Fu C, Bannister B, Kong SX, Jhaveri J, et al. Drug-drug interaction potential among patients with nonmetastatic castration-resistant prostate cancer (nmCRPC) treated with novel androgen receptor inhibitors. Expert Rev Anticancer Ther. 2024;24(5):325-33.
69. Conde-Estévez D, Henríquez I, Muñoz-Rodríguez J, Rodriguez-Vida A. Treatment of non-metastatic castration-resistant prostate cancer: facing age-related comorbidities and drug–drug interactions. Expert Opinion on Drug Metabolism & Toxicology. 2022;18(9):601-13.
70. Boujonnier F, Lemaitre F, Scailteux L-M. Pharmacokinetic Interactions Between Abiraterone, Apalutamide, Darolutamide or Enzalutamide and Antithrombotic Drugs: Prediction of Clinical Events and Review of Pharmacological Information. Cardiovascular Drugs and Therapy. 2023.
71. Park SJ, Yoder B, Li T. Comparison of second-generation antiandrogens for the treatment of prostate cancer. Journal of Hematology Oncology Pharmacy. 2022;12(2).
72. Leblanc K, Edwards SJ, Dranitsaris G, Leong DP, Carrier M, Malone S, et al. Drug Interactions between Androgen Receptor Axis-Targeted Therapies and Antithrombotic Therapies in Prostate Cancer: Delphi Consensus. Cancers (Basel). 2024;16(19).
73. Bolek H, Yazgan SC, Yekeduz E, Kaymakcalan MD, McKay RR, Gillessen S, et al. Androgen receptor pathway inhibitors and drug-drug interactions in prostate cancer. ESMO Open. 2024;9(11):103736.
74. BNF. British National Formulary: Darolutamide drug interactions 2025 [Available from: https://bnf.nice.org.uk/interactions/darolutamide/.
75. EMA. Summary of Product Characteristics. Daralutamide (NUBEQA) 2024 [updated 20-Dec-2024. Available from: https://www.medicines.org.uk/emc/product/11324/smpc/print.
76. EMA. Summary of Product Characteristics: enzalutamide (Xtandi) 2018 [updated 8 February 2018. Available from: https://www.ema.europa.eu/en/documents/product-information/xtandi-epar-product-information_en.pdf.
77. EMA. Summary of Product Characteristics: apalutamide (Erleada) 2023 [updated 22 September 2023. Available from: https://www.ema.europa.eu/en/documents/product-information/erleada-epar-product-information_en.pdf#:~:text=Treatment%20with%20apalutamide%20should%20be%20initiated%20and%20supervised,mg%20tablets%29%20as%20an%20oral%20single%20daily%20dose.
78. EMA. Summary of Product Characteristics: relugolix (Orgovyx 120 mg film-coated tablets) 2022 [updated 29 April Available from: https://www.ema.europa.eu/en/documents/product-information/orgovyx-epar-product-information_en.pdf.
79. BNF. Relugolix Drug Monograph: Interactions [Available from: https://bnf.nice.org.uk/interactions/relugolix/.
80. Gillessen S, Turco F, Davis ID, Efstathiou JA, Fizazi K, James ND, et al. Management of Patients with Advanced Prostate Cancer. Report from the 2024 Advanced Prostate Cancer Consensus Conference (APCCC). Eur Urol. 2025;87(2):157-216.

81. Zheng J, Sampurno F, George DJ, Morgans AK, Nguyen H, Abrahm JL, et al. Establishing metastatic prostate cancer quality indicators using a modified Delphi approach. Clin Genitourin Cancer. 2022;20(2):e151-e7.
82. Graham LS, Lin JK, Lage DE, Kessler ER, Parikh RB, Morgans AK. Management of Prostate Cancer in Older Adults. Am Soc Clin Oncol Educ Book. 2023;43:e390396.
83. Loh KP, Liposits G, Arora SP, Neuendorff NR, Gomes F, Krok-Schoen JL, et al. Adequate assessment yields appropriate care-the role of geriatric assessment and management in older adults with cancer: a position paper from the ESMO/SIOG Cancer in the Elderly Working Group. ESMO Open. 2024;9(8):103657.
84. de Freitas HM, Ito T, Hadi M, Al-Jassar G, Henry-Szatkowski M, Nafees B, et al. Patient Preferences for Metastatic Hormone-Sensitive Prostate Cancer Treatments: A Discrete Choice Experiment Among Men in Three European Countries. Adv Ther. 2019;36(2):318-32.
85. Gonzalez JM, Ganguli A, Morgans AK, Tombal BF, Hotte SJ, Suzuki H, et al. Discrete-Choice Experiment to Understand the Preferences of Patients with Hormone-Sensitive Prostate Cancer in the USA, Canada, and the UK. Patient. 2023;16(6):607-23.
86. Menges D, Piatti MC, Omlin A, Cathomas R, Benamran D, Fischer S, et al. Patient and General Population Preferences Regarding the Benefits and Harms of Treatment for Metastatic Prostate Cancer: A Discrete Choice Experiment. Eur Urol Open Sci. 2023;51:26-38.
87. George DJ, Ganguli A, Morgans AK, et al. Patient preferences for treatment and outcomes in hormone-sensitive prostate cancer (HSPC). Journal of Clinical Oncology. 2022;40(16_suppl):e18757-e.
88. Ozturan D, Morova T, Lack NA. Androgen Receptor-Mediated Transcription in Prostate Cancer. Cells. 2022;11(5).
89. Baumgart SJ, Nevedomskaya E, Lesche R, Seidel H, Haendler B. A detailed comparison between second-generation AR antagonists reveals differences in the overall impact on gene regulation patterns in prostate cancer cells. Cancer Res. 2018;78:1798.
90. Fizazi K, Smith MR, Tombal B. Clinical Development of Darolutamide: A Novel Androgen Receptor Antagonist for the Treatment of Prostate Cancer. Clinical genitourinary cancer. 2018;16(5):332-40.
91. Weaver CH. Understanding side effects of androgen deprivation therapy: Cancer Connect; 2023 [Available from: https://news.cancerconnect.com/prostate-cancer/understanding-side-effects-of-androgen-deprivation-therapy.
92. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.
93. Cleeland CS. The Brief Pain Inventory User Guide 2009.
94. Fizazi K, Shore N, Tammela TL, Ulys A, Vjaters E, Polyakov S, et al. Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med. 2019;380(13):1235-46.
95. Higano C. Enzalutamide, apalutamide, or darolutamide: are apples or bananas best for patients? Nat Rev Urol. 2019;16(6):335-6.
96. Williams SCR, Mazibuko N, O'Daly O, Zurth C, Patrick F, Kappeler C, et al. Comparison of Cerebral Blood Flow in Regions Relevant to Cognition After Enzalutamide, Darolutamide, and Placebo in Healthy Volunteers: A Randomized Crossover Trial. Target Oncol. 2023;18(3):403-13.
97. Wang L, Lu B, He M, Wang Y, Wang Z, Du L. Prostate Cancer Incidence and Mortality: Global Status and Temporal Trends in 89 Countries From 2000 to 2019. Front Public Health. 2022;10:811044.
98. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-49.

99. Vince RA, Jr., Jiang R, Bank M, Quarles J, Patel M, Sun Y, et al. Evaluation of Social Determinants of Health and Prostate Cancer Outcomes Among Black and White Patients: A Systematic Review and Meta-analysis. JAMA Netw Open. 2023;6(1):e2250416.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost Comparison Appraisal

Darolutamide with androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer [ID6452]

Clarification questions

April 2025

File name	Version	Contains confidential information	Date
ID6452 darolutamide for mHSPC Clarification questions_230525[Redacted]	1	No	23/05/25

Section A: Clarification on effectiveness data

Choice of comparator

A1. PRIORITY QUESTION. Please elaborate further on the choice of comparator treatment for cost comparison. Specifically, the reasons for not including enzalutamide + ADT as a comparator.

Bayer have compared darolutamide + ADT with apalutamide + ADT, as it is the only appropriate comparator for this appraisal. Unlike enzalutamide + ADT, apalutamide + ADT is used in the same docetaxel ineligible population as proposed for darolutamide + ADT. Apalutamide + ADT also has BlueTeq restrictions on patient population that would be applicable to darolutamide + ADT.

This approach was discussed with the NICE and EAG teams at the decision problem meeting for this appraisal, where NICE confirmed that one only NICE approved comparator was required in a cost-comparison appraisal. Furthermore, for cost-comparison analyses, paragraph 2.6.1 of the NICE manual states "*The chosen comparator must be established in practice and have substantial use in the NHS in England for the same indication*". Apalutamide + ADT is a widely used in the treatment of mHSPC, with BlueTeq data indicating that approximately [redacted] patients were treated apalutamide + ADT for mHSPC in 2024, equating to approximately [redacted] of ARTA use in this indication.[1]

The use of apalutamide + ADT as the comparator within this submission, was also discussed and validated with UK clinical experts at a recent advisory board where consensus was reached that the patient populations for both treatments are comparable in terms of disease status, age, and co-morbidities.[2]

ARANOTE trial

A2. Please supply the study protocol (most up to date version) and the final statistical analysis plan for the ARANOTE trial.

These have been provided as separate documents.

A3. We note the primary endpoint rPFS and secondary endpoints (other than OS) are from the primary completion analysis DCO Jun 7, 2024 (reported in a clinical study report), and the OS and safety data are from the final OS analysis DCO [redacted], (reported in a summary clinical study report). In addition to the OS and safety data, were further follow-up data for the primary and secondary endpoints available at the final OS DCO [redacted]? If so, please provide these (e.g. in an updated clinical study report).

As per the ARANOTE study protocol (provided in response to A2), the final rPFS analysis was performed at the primary completion cut-off data (Jun 7, 2024). Within the open-label (OL) phase of the study, assessment of participants continued with recording of survival status plus standard safety assessments (adverse events [AEs], electrocardiograms, vital signs, and laboratory safety assessments and Eastern Cooperative Oncology Group [ECOG] assessments).

The collection of data related to other prespecified efficacy endpoints was no longer required per protocol and as such only OS and safety data are available from the final OS data cut ([redacted]).

A4. Please update Figure 2 in CS Appendix D.1.2 to include participant disposition in ARANOTE at the time of final OS analysis, or describe patient disposition up until the final data cut off.

Following treatment unblinding at the time of primary completion, all participants still on study treatment (darolutamide or placebo) were offered the opportunity to start darolutamide treatment within the OL. Subsequently, [redacted] participants who were ongoing in the placebo arm crossed-over to OL darolutamide treatment with [redacted] initiating OL darolutamide. Please find below the summary of participant disposition by treatment period available at the time of final OS analysis (Figure 1) and for completeness a summary of reasons for study drug discontinuation is presented in Table 2.

Figure 1. Summary of participant disposition by treatment period

Abbreviations: CO, Cross-over; DB, Double-blind; FAS, Full analysis set; FPFV, First patient first visit; N, Total number of participants; OL, Open-label; OS, Overall survival; SAF, Safety analysis set

Note: During the Darolutamide DB period and the Darolutamide DB+OL period, 3 of the 446 participants randomised to darolutamide did not start study treatment (included in FAS but not SAF). Also, during the Darolutamide DB period and the Darolutamide DB+OL period, 3 participants randomised to placebo received both placebo and at least 1 dose of darolutamide by mistake (included in placebo for FAS but darolutamide for SAF). For the Placebo-darolutamide CO period, [redacted] participants signed informed consent (included in the FAS), [redacted] participants started OL darolutamide; however, 1 of these [redacted] participants received darolutamide by mistake during the Darolutamide DB period. Therefore, for the SAF, this participant is included under darolutamide for the Darolutamide DB and Darolutamide DB+OL periods rather than in the Placebo-darolutamide CO

Table 1. Study Drug Discontinuations in ARANOTE

Number of participants (n, %)	Darolutamide + ADT (DB) N=446	Darolutamide + ADT (DB & OL) N=446	Placebo + ADT (DB) N=223)	Placebo-Darolutamide (crossover period) N=[redacted]
Started study drug[a]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued study drug	[redacted]	[redacted]	[redacted]	[redacted]
Primary reason:				
• Progressive disease - central radiological assessment	[redacted]	[redacted]	[redacted]	[redacted]
• Progressive disease - clinical assessment	[redacted]	[redacted]	[redacted]	[redacted]
• Withdrawal by subject	[redacted]	[redacted]	[redacted]	[redacted]
• Adverse event not associated with clinical disease progression	[redacted]	[redacted]	[redacted]	[redacted]
• Subject decision	[redacted]	[redacted]	[redacted]	[redacted]
• Progressive disease - local radiological assessment	[redacted]	[redacted]	[redacted]	[redacted]
• Adverse event associated with clinical disease progression	[redacted]	[redacted]	[redacted]	[redacted]
• Death	[redacted]	[redacted]	[redacted]	[redacted]
• Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]
• Physician decision: rising PSA value	[redacted]	[redacted]	[redacted]	[redacted]
• Required study drug interruption longer than allowed per protocol	[redacted]	[redacted]	[redacted]	[redacted]
• Physician decision	[redacted]	[redacted]	[redacted]	[redacted]
• Other	[redacted]	[redacted]	[redacted]	[redacted]
• Additional primary malignancy	[redacted]	[redacted]	[redacted]	[redacted]
• Non-compliance with study drug	[redacted]	[redacted]	[redacted]	[redacted]
• Subject decision: rising PSA value	[redacted]	[redacted]	[redacted]	[redacted]
Ongoing with study drug (as of the database cut-off date)	[redacted]	[redacted]	[redacted]	[redacted]

[a]: All participants, with the exception of one, received ADT during treatment and/or had orchiectomy.
[b]:1 participant did not start treatment
Note: 3 participants randomised to the placebo arm but received any dose of darolutamide through wrong kits assignment and therefore they were analysed under darolutamide arm as treated in the safety analysis set.

A5. PRIORITY QUESTION. Please report the procedures for crossover adjustments to the ARANOTE trial final OS data for the rank preserving structural failure time (RPSFT) and the iterative parameter estimation (IPE) methods.

The data cutoff of final OS analysis ([redacted]) occurred [redacted] months after the primary completion (07 June 2024), therefore, the period of crossover for the final OS analysis was [redacted]. There were [redacted] deaths were reported in the final OS analysis database after primary completion ([redacted] in the darolutamide arm, [redacted] in the placebo arm). As reported in response to A4, there were [redacted] randomised placebo subjects crossed over to darolutamide after primary completion. Out of these [redacted] subjects only [redacted] died under the darolutamide crossover period. Therefore, the impact of crossover in OS was minimum.

To adjust for the effect of crossover from placebo to darolutamide on the OS endpoint, the OS data were analysed using two different adjustment methods: rank preserving structural failure time (RPSFT) and iterative parameter estimation (IPE). The adjustment methods estimate the treatment effect as if patients in the placebo arm had never switched to darolutamide treatment. The adjusted analyses were performed as sensitivity analyses. The results from both crossover adjustment methods are consistent with the main OS results.

- RPSFT is a method that adjusts for the crossover effect by using a model that preserves the rank order of failure times, this method recalculates the censoring by applying a treatment effect for crossover. It essentially re-estimates the failure times under the assumption that patients who crossed over would have had the same outcomes as those who did not.
- RPSFT result: [redacted]

Table 2:

[redacted]

- IPE uses inverse probability weighting to adjust for the treatment effects by weighting observations based on the probability of receiving the treatment they actually received.
- IPE result: [redacted]

Table 3:

[redacted]

A6. Please explain the selection process for crossover trial adjustment methods in the ARANOTE trial. Specifically, the rationale for using the rank preserving structural failure time (RPSFT) and iterative parameter estimation (IPE) methods, in preference to other available methods (e.g. Inverse Probability of Censoring Weights (IPCW)).

The RPSFT and IPE methods, which are two well-known randomisation-based methods for estimating counterfactual survival times in the presence of crossover, were pre-planned per statistical analyses plan. In fact, recent research into the cross-over methodology included in NICE appraisals, found that RPSFT was the most highly used approach, included in 11 out of the 19 appraisals where cross-over analysis has been submitted.[3]

Bayer understands that other methods were available and could have been used, all such methods are subject to limitations. However, it should be noted that the cross-

over adjusted outcomes from RPSFT and IPE methods were very similar which provides confidence that the appropriate methodologies have been applied for these analyses.

A7. If available, please report the final OS results based on crossover adjustments for all other available methods (e.g. as per NICE DSU Technical support document TSD 16: 'Adjusting survival time estimates in the presence of treatment switching').

Please note that only RPSFT and IPE methodology was considered within the crossover adjustment, and no other method was performed, as there were very few OS events [redacted] documented between primary completion and final OS analysis. The final OS data cut-off was only [redacted] after primary completion cut-off date.

A8. Were any adjustments made to OS, or any other outcomes, to account for the effects of subsequent treatments received by patients in the ARANOTE trial? For example, to remove subsequent treatments not relevant to current clinical practice in the NHS. Please provide methods and results of any such adjustments made.

Please note that there was no adjustment made to patient-level OS data for analysis. As per the study protocol, if a patient received subsequent treatment before death, the death was still considered as an event. For the primary endpoint (rPFS) events documented after start of subsequent anti-cancer treatment were censored at the last scan prior to the start of a new anti-cancer treatment.

It was demonstrated in the previous submission for darolutamide + docetaxel +ADT in first-line treatment of mHSPC[4] (CS Section B3.5.3.1), that the subsequent treatments received following treatment with darolutamide are unlikely to affect the observed survival. The post-hoc analysis of darolutamide and docetaxel post-progression survival (PPS) from ARASENS, stratified per subsequent treatment demonstrated that there was no difference in PPS observed between patients receiving an ARTA, or another subsequent treatment in patients in the darolutamide arm (Figure 2). In contrast, for the docetaxel arm, a clear PPS benefit was observed for patients receiving either abiraterone or enzalutamide (Figure 3). As both ARANOTE and ARASENS investigate the use of first-line use of darolutamide in mHSPC, there is no clear clinical rationale for this observation not to be applicable to

ARANOTE, as such there would be limited impact of subsequent treatments on the efficacy demonstrated by darolutamide + ADT.

Figure 2:

Abbreviation: ADT, androgen deprivation therapy

Figure 3:

Abbreviation: ADT, androgen deprivation therapy

A9. PRIORITY QUESTION. The company's preferred position for darolutamide + ADT in the mHSPC care pathway is for the treatment of patients who are ineligible for chemotherapy (docetaxel). The EAG notes that patients who had previously received chemotherapy including docetaxel for prostate cancer were ineligible to enrol in the ARANOTE trial. However, it is unclear whether patients not previously treated with docetaxel who enrolled in the trial are necessarily docetaxel ineligible in

clinical practice. The CS does not explicitly refer to the trial population as being docetaxel eligible or ineligible. Please outline the characteristics of the ARANOTE study population which can be considered contraindications to docetaxel (e.g. factors such as poor overall performance status, poor bone marrow func##tion due to extensive disease as listed in CS page 22, CS Section B.1.3.1.)

Eligibility for docetaxel extends beyond the presence of contraindications and is determined by a range of clinical and non-clinical factors. For example, NICE technology appraisal guidance such as TA721 'abiraterone for newly diagnosed high-risk hormone sensitive metastatic prostate cancer' notes that "many factors" affect eligibility for docetaxel and that "one of these is patient choice after hearing the risks and benefits of each available treatment". Patients deemed ineligible or unsuitable for docetaxel may include those with significant frailty, multiple comorbidities, or limited access to treatment due to geographical, logistical, or social barriers. Additional considerations include the patient's preference, their psychological and emotional wellbeing, caregiver support, and broader socioeconomic factors.

Nonetheless, within ARANOTE the rPFS benefit for darolutamide was consistently observed across all prespecified subgroups (original CS Section B.3.7), including Eastern Cooperative Oncology Group (ECOG) performance status and age. These are characteristics which have been noted to make patients more likely to be ineligible or unsuitable for chemotherapy. Furthermore, the majority of the patients in the ARANOTE study (91.3% in the darolutamide arm and 93.3% in the placebo arm) had at least one comorbidity upon study entry, as noted above the presence of comorbidities is to be considered as part of eligibility for docetaxel decision making as per the BlueTeq criteria. The most common comorbidities with the ARANOTE populations were vascular disorders, musculoskeletal and connective tissue disorders, renal and urinary disorders and metabolism and nutrition disorders. Taken together, it can be seen that evidence that ARANOTE trial is applicable to patients with mHSPC.

Criteria for identifying patients who are suitable for treatment with apalutamide and therefore unsuitable for docetaxel are outlined in apalutamide BlueTeq form (excerpt below) which also emphasises the critical role of clinical judgment in assessing the

appropriateness of docetaxel on an individual patient basis and also informed patient preference. Given that darolutamide will be considered in the same position as apalutamide, Bayer consider it would be appropriate to use these criteria to identify docetaxel-ineligible/unsuitable patients for the purposes of guidance for darolutamide.

Excerpt from Apalutamide BlueTeq

The prescribing clinician has assessed patient status with regards to receiving upfront docetaxel and has concluded the patient is ineligible on the grounds of either having significant comorbidities (i.e. the patient should not be treated with docetaxel), or the patient is fit for upfront docetaxel but, after fully informed consent, has chosen not to receive upfront docetaxel.

- *The patient has significant comorbidities which preclude treatment with docetaxel (i.e. **the patients SHOULD NOT be treated with docetaxel**) and this has been fully discussed with the patient.*
    - *It is recommended that validated systems of scoring clinical frailty are used as part of the oncology assessment as to explaining the benefits and risks of the treatment options of chemotherapy and apalutamide*
- *The patient is fit for chemotherapy with docetaxel and has chosen not to be treated with docetaxel. The patient has been fully consented regarding the following: the advantages and disadvantages of upfront docetaxel v upfront apalutamide, that the use of upfront apalutamide would results in there being no further possible treatment with any androgen receptor targeted agents when the patient's disease progresses; and that the patient may not be fit enough to receive docetaxel when the patient's disease progresses. After such informed consent, the patient has chosen to receive upfront apalutamide (i.e. **the patient is fit for chemotherapy with docetaxel and has CHOSEN NOT to be treated with docetaxel**)*

Network meta-analysis (NMA)

A10. Was a feasibility assessment for the NMA performed? Please give details of the methods and results of any feasibility assessment over and above the details currently given at the start of CS section B.3.9 (notwithstanding the feasibility

assessment for a quantitative analysis of the surrogacy relationship between rPFS and OS in patients with mHSPC mentioned in Appendix J1.2))

Please note that there was additional feasibility analysis presented within the Appendix Section D1.1.2 and Section D1.3

- Tables 16 - Comparing trial designs of studies included in NMA
- Table 17 - Comparing outcome reporting of studies included in NMA
- Table 18 - Outcome definitions of studies included in NMA (comparing PFS outcome definition)
- Table 19 - Comparing target populations of studies included in NMA
- Table 20 - Completed NICE methodology checklist for RCTs to assess the quality of the TITAN publication

A11. Please expand the list of study characteristics in CS Table 14 in section B.3.9 to include other relevant characteristics, particularly known prognostic factors and effect modifiers in mHSPC.

We have provided a comprehensive list of study characteristics which cover the prognostic factors and effect modifiers in mHSPC. We believe the list covers all the key aspects and do not have any additional characteristics to add.

A12. Was any consideration given to including studies of other treatments for mHSPC in the in the network meta-analysis, specifically to increase sample size and boost statistical power? For example, inclusion of other trials with an ADT + placebo arm?

Additional studies are only needed in an NMA if they give direct or indirect evidence on the relative treatment effects of the comparators of interest, so having an ADT + placebo arm is not sufficient to justify inclusion. We did not identify any other study which included such direct or indirect evidence for the comparison between darolutamide + ADT and apalutamide + ADT, therefore the most appropriate analysis for this submission is between the ARANOTE and TITAN studies.

A13. Please clarify the source publications of the TITAN trial data in CS Appendix Tables 21-25 and from which analysis set (i.e. primary, interim, final) of the TITAN trial they are from.

We have included an extra column named "analysis set" to highlight the analysis set i.e., primary vs final, used within each analysis

Table 21: rPFS results from trials included in NMA

Study	Treatment 1	Treatment 2	HR (95% CI)	Median follow up (months)	Analysis set
ARANOTE	Darolutamide + ADT	ADT	0.541 (0.413, 0.707)	25.0	Primary [5]
TITAN	Apalutamide + ADT	ADT	0.48 (0.39, 0.60)	22.7	Primary[6]

Abbreviations: HR, hazard ratio; OS, overall survival; CI, confidence interval; rPFS, radiographic progression-free survival

Table 22: OS results from trials included in NMA

Study	Treatment 1	Treatment 2	HR (95% CI)	Median follow up (months)	Analysis set
ARANOTE	Darolutamide + ADT	ADT	[redacted]	[redacted]	Final[7]
TITAN	Apalutamide + ADT	ADT	0.65 (0.53, 0.79)	44.0	Final[8]

Abbreviations: HR, hazard ratio; OS, overall survival; CI, confidence interval; rPFS, radiographic progression-free survival

Table 23: Input data for time to deterioration in FACT-P total score

Study ID	Treatment 1	Treatment 2	HR (95%CI)	Median OS follow up (months)	Analysis set
ARANOTE	Darolutamide + ADT	ADT	0.76 (0.61, 0.94)	25.00	Primary[9]
TITAN	Apalutamide + ADT	ADT	1.02 (0.85, 1.22)	22.70	Primary[6]

Abbreviations: HR, hazard ratio; OS, overall survival; CI, confidence interval; FACT-P, Functional Assessment of Cancer Therapy – Prostate

Table 24: Input data for grade 3-5 AEs

Study ID	t1	t2	r1	n1	r2	n2	E1	E2	Median follow up arm 1*	Median follow up arm 2*	Analysis set
ARANOTE	DAR+ADT	ADT	166**	446	81	220	14004.4	6710	31.4	30.5	Final[7]
TITAN	APA+ADT	ADT	279	524	237	527	23056	23188	44.0	44.0	Final[8†]

Abbreviations: r, number of events; t, treatment; n, number of patients in arm; E, exposure time (= number of patients in arm multiplied by mean follow-up). *OS median follow up in months used as it is the follow up time available in both studies. **Number of events during both the double blind and open label periods for the darolutamide + ADT arm; †Data is reported in Supplementary Table S3

Table 25: Input data for discontinuation due to AEs

Study ID	t1	t2	r1	n1	r2	n2	E1	E2	Median follow up arm 1*	Median follow up arm 2*	Analysis set
ARANOTE	DAR+ADT	ADT	28	446	20	220	14004.4	6710	31.4	30.5	Final[7]
TITAN	APA+ADT	ADT	62	524	30	527	23056	23188	44.0	44.0	Final[8†]

Abbreviations: r, number of events; t, treatment; n, number of patients in arm; E, exposure time (= number of patients in arm multiplied by mean follow-up). *OS median follow up in months used as it is the follow up time available in both studies. †Data is reported in Supplementary Table S3

A14. Please clarify if the NMA input data and NMA results for the Grade 3-5 AEs outcome is for all Grade 3-5 AEs or if they are limited to Grade 3-5 AEs in ≥5% of participants as reported in CS section B.3.10 for ARANOTE.

The NMA input data and NMA results for the Grade 3-5 AEs are for all Grade 3-5 AEs and they are not limited to those in the ≥5% of participants.

A15. Please provide the Openbugs programming code used in the NMA.

These have been provided as separate documents

General questions

A16. We note that there is an ongoing open-label company trial, set in the US, of darolutamide + ADT vs a matched historical control arm of ADT alone (derived from the CHAARTED RCT) for treating men with mHSPC (the ARASEC trial). According

to ClinicalTrials.gov the estimated primary completion date is 15-04-2025. Please confirm when the results will be available.

The ARASEC study is still ongoing and has not reached primary completion date yet, it is expected to be reached [redacted] with data availability in [redacted].

Section B: Clarification on cost-effectiveness data

Economic model

B1. PRIORITY QUESTION. Please consider providing an updated cost-comparison model that includes: i) clinical efficacy (e.g. survival estimates including PFS and OS); ii) costs (including, drug acquisition, drug administration, resource use, subsequent treatments, adverse events); iii) safety outcomes (e.g. adverse events); and iv) mortality. The company's economic model includes only drug acquisition costs, and the EAG are unable to test the impact of varying the parameter inputs such as resource use, subsequent treatments, adverse events, etc. on the overall cost-comparison results.

Darolutamide + ADT for the treatment of mHSPC is assessed through the cost-comparison route. As presented in the NMA in CS Section B.3.9, there is no evidence of a difference in rPFS and OS between darolutamide + ADT and apalutamide + ADT which justifies the use of a cost-comparison analysis.

Including clinical efficacy in the analysis would not have any impact on the results, as they can be considered equally effective. Additionally, if efficacy between the two treatments would be assumed to differ, the analysis would no longer be a cost-comparison analysis.

The costs currently included in the cost-comparison analysis are drug acquisition and administration costs. As darolutamide + ADT and apalutamide are both ARTAs, and have the same place in the treatment algorithm, subsequent treatment is expected to be the same after either of these treatments. Therefore, adding subsequent treatment to the analysis would not result in any further difference between the arms as the costs would be the same in both arms.

As discussed in CS Section B.4.2.5, resource use is broadly expected to be similar between the arm, therefore the inclusion of resource use within the model is not considered to have a significant impact on the results of the economic analysis. It should be noted that darolutamide + ADT is associated with a reduction potential DDIs allowing for simplified treatment decisions and reducing the need for coordination between healthcare providers, which may result in a slightly reduced health care resource use compared to apalutamide. Furthermore, patients treated with apalutamide require thyroid function tests, adding extra monitoring steps and increasing healthcare resource utilisation. This involves additional tests, follow-ups, and coordination between healthcare providers. Both the reduced DDIs and lack of thyroid testing associated with the use darolutamide + ADT is expected to lead to a reduction in health care resource use compared the treatment with apalutamide + ADT. In addition, darolutamide + ADT is associated with reduced AEs as presented in Table 2, and further demonstrated through the results of the NMA (rate ratio for grade 3-5 AEs vs apalutamide + ADT [redacted]), which will result in reduced costs in the darolutamide + ADT arm compared to the darolutamide + ADT arm. By not modelling the potential cost-saving through reduced health-care resource use and adverse events associated with darolutamide + ADT, the analysis can be considered conservative.

Table 4: Summary of adverse events for darolutamide + ADT and apalutamide + ADT

Adverse event, n (%)	Darolutamide + ADT (n=445)[5]	Apalutamide + ADT (n=524)[6]
Any AE	405 (91.0)	507 (96.8)
Serious AE	105 (23.6)	104 (19.8)
Grade 3 or 4 AE	137 (30.8)	221 (42.2)
AE leading to permanent discontinuation of study drug	27 (6.1)	42 (8.0)
AEs of special interest – all grades		
Hot flushes	41 (9.2)	119 (22.7)
Rash	19 (4.3)	142 (27.1)
Falls	6 (1.3)	39 (7.4)
Fracture	18 (4.0)	33 (6.3)
Fatigue	25 (5.6)	103 (19.7)

Abbreviations: ADT: Androgen Deprivation Therapy; AEs: Adverse events.

B2. Please clarify the source of the Kaplan Meier curve for PFS figure in Sheet!Cost-comparison of the Excel model. Does the Kaplan Meier curve represent the rPFS from the ARANOTE trial?

Yes, the Kaplan-Meier curve in the cost-comparison model does indeed represent rPFS from the ARANOTE trial.

Proportions and costing of ADT

B3. CS Section B.4.2.3: The EAG note inconsistencies in the reporting of ADT proportions in the CS and the model (see Table 1). Please clarify which estimates are appropriate.

Table 5 Proportions for ADT reported in the CS and the model

ADT	CS	Economic model
Degarelix (initial injection)	Not reported	12.6%
Degarelix (subsequent injections)	Not reported	12.6%
Leuprorelin	30%	54%
Goserelin	30%	31.9%
Triptorelin	40%	1.5%
Buserelin	Not reported	0.0%

We thank the EAG for pointing out this inconsistency between the model and CS document. The values reported in the CS are the correct ones and are based on the proportions for ADT used in the assessment of darolutamide with ADT and docetaxel for treating mHSPC, as presented in Table 29 of the company submission for TA903.[4]

We have corrected the values in the cost-comparison model. This reduces the per cycle costs of ADT acquisition costs (from £119.30 to £68.09) and administration costs (from £435.98 to £238.96) but has no impact on the results of the analysis as patients in both arms are assumed to have the same duration of treatment with ADT.

B4. CS Section B.4.2.3: The EAG notes that the ADT acquisition costs were not provided in the CS (see CS B.4.2.3, page 96) but were modelled and considered in directly in the economic model. Please provide a table with the ADT acquisition costs and regimen for completeness.

Please see the relevant ADT dosing regimens and costs per model cycle in Table 4.

Table 6: ADT regimens and acquisition costs

Treatment	Dose	Cost per dose	Dosing frequency	Units per model cycle	Acquisition costs per cycle
Leuprorelin	3.75 mg	£69.60	1 per 30 days	0.93	£64.96
Goserelin	3.60 mg	£70.00	1 per 28 days	1	£70.00
Triptorelin	3.00 mg	£69.00	1 per 28 days	1	£69.00

Section C: Textual clarification and additional points

C1. Please supply an abbreviations list for CS document B.

ID6452_darolutamide%20ADT%20mHSPC_T

C2. CS Section B.4.2.1 The CS states the mean age of ARANOTE ITT population is 69 years. However, the economic model uses 69.67 years as the starting point in the patient flow and cost calculation. Please clarify which estimate is correct.

The mean age of 69 from the ARANOTE trial is correct. We have adjusted the cost-comparison model to also use 69 years as the starting age. This has no impact on the model outcomes.

References

1. Bayer. Blueteq data - Annual ARTA usage in mHSPC [Data on file]. 2025 27th January 2025.
2. Bayer AG. ARANOTE Advisory Board Meeting: Understanding the future metastatic hormone sensitive prostate cancer (mHSPC) landscape. Bayer AG; 2024 6 December 2024.
3. Kijauskaite G, Jones C, McKendrick J. HTA106 How Has Treatment Switching Been Accounted for? Insights From NICE Appraisals. Value in Health. 2024;27(12):S374.
4. National Institute for Health and Care Excellence. Darolutamide with androgen deprivation therapy and docetaxel for treating hormone-sensitive metastatic prostate cancer. Technology appraisal guidance [TA903]. 2023 [Available from: https://www.nice.org.uk/guidance/ta903.
5. Saad F, Vjaters E, Shore M, Olmos D, Xing N, Pereira de Santana Gomes AJ, et al. Darolutamide in Combination With Androgen-Deprivation Therapy in Patients With Metastatic Hormone-Sensitive Prostate Cancer From the Phase III ARANOTE Trial. ESMO September 16, 2024. J Clin Oncol. 2024; 00:1-11.
6. Chi KN, Agarwal N, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, et al. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med. 2019;381(1):13-24.
7. Bayer AG. Final Overall Survival Results Summary for Study 21140 (ARANOTE): A randomized, double-blind, placebo-controlled Phase 3 study of darolutamide in addition to androgen deprivation therapy (ADT) versus placebo plus ADT in men with metastatic hormone-sensitive prostate cancer (mHSPC). 2025.
8. Chi KN, Chowdhury S, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, et al. Apalutamide in Patients With Metastatic Castration-Sensitive Prostate Cancer: Final Survival Analysis of the Randomized, Double-Blind, Phase III TITAN Study. J Clin Oncol. 2021;39(20):2294-303.
9. Bayer. Clinical Study Report: Phase 3 study of darolutamide in addition to ADT versus placebo plus ADT in men with mHSPC (ARANOTE). 2024.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Darolutamide with androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer [ID6452]

Patient Organisation Submission

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

1.Your name	[redacted]
2. Name of organisation	Prostate Cancer Research
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Prostate Cancer Research is a research and patient engagement organisation focused on advancing ground-breaking research and interventions into diagnosis, treatment, and care to create a future where prostate cancer no longer threatens lives. Our focus is on delivering innovative solutions and improving quality of life for patients, families, and communities affected by prostate cancer, and supporting and encouraging marginalised and underrepresented communities to be part of the positive changes we are working to achieve in research, treatment and care. To achieve this, our team of 38 members of staff are focused on four core programmes of work: 1. Academic and social research funding aimed at groundbreaking advances in preventing, diagnosing, and treating advanced prostate cancer and enhancing patient quality of life; 2. Translational research, bridging the gap between industry, investors, health providers, and patients, supporting diagnostics and treatments to progress from laboratory to patient; 3. Patient information and empowerment, giving marginalised and traditionally underrepresented individuals with prostate cancer a greater role in shaping research, treatment, and care; 4. Policy and advocacy, seeking to ensure greater equity of treatment and parity of care, and working towards a world where no one affected by prostate cancer is left behind

	PCR's work is funded through diverse income streams. We are focused on accessing significant restricted funding through Trusts & Foundations, Statutory, Corporates and Major Donors, while at the same time ensuring we have flexible and sustainable funding through our Events & Community, Legacies and Individual Giving fundraising. PCR is not a membership organisation but works with thousands of patients across its various charitable activities. In the two years since we launched the infopool, an educational website to support and empower patients, we have had close to 250,000 visitors. Since launching Prostate Progress, our patient data platform, in July 2024 we have over 4,000 consented patients signed up to the platform sharing PROMs data and consenting to link their clinical data.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	We received £1,260 in October 2024 from Bayer. The purpose of this funding was to pay for our CEO's time for participation and preparation for a policy roundtable on health inequalities.
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	For personalised information and support, the infopool offers resources tailored to individuals living with prostate cancer. This platform provides insights into treatment options, side effect management,

experiences of patients and carers to include in your submission?	and personal stories from others navigating similar experiences. Patient stories collected through the infopool give valuable insights into patient experience and preferences. We have over 1,000 stories from individuals on the site which have helped inform our submission. Additionally, we conducted an online 'Patient Experience Survey' hosted on PCR's website for a period of two weeks in January 2022. The aim of this survey was "To better understand patients' disease journeys, information needs and impact on their quality of life." Insights from this survey have also informed our submission.

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?	Living with hormone-sensitive metastatic prostate cancer (mHSPC) means facing the challenges of both the disease itself and the side effects of its treatment. While androgen deprivation therapy (ADT) can be effective, it often comes with a range of side effects, including hot flashes, tiredness, loss of muscle and bone strength, sexual difficulties, and an increased risk of conditions like diabetes and heart disease. Beyond the physical effects, the emotional and psychological impact of mHSPC can be significant. Many patients experience feelings of anxiety, sadness, or depression as they adjust to life with cancer and its treatment. The disease doesn't just affect those diagnosed – it also has a profound impact on family members and loved ones.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Patients with prostate cancer value and appreciate access to effective treatments as well as the care and support they receive from NHS oncology teams, urologists, specialist nurses and GPs. They value being able to access oral treatments that can be taken at home. However, many feel frustrated that treatment choices are limited and would like more flexibility to personalised care based on side effects, lifestyle or preferences. Some patients report that care can feel disjointed, and their mental health and sexual function needs have been overlooked.

8. Is there an unmet need for patients with this condition?	Darolutamide plus ADT directly addresses several of the most important unmet needs in the treatment of mHSPC – improving survival, delaying disease progression, minimising side effects, and expanding treatment options. It's important to recognise that not every patient with mHSPC is the same. Introducing darolutamide plus ADT would provide patients and clinicians with greater choice, support more personalised care, enable shared decision-making, and align with NHS priorities around patient-centred treatment. Fatigue is a major concern for men with mHSPC, affecting around 30-40% of patients. Whilst fatigue is a common side effect of treatments like ADT, it may arise as a direct symptom of the cancer itself, independent of treatment. Its severity and impact can vary considerably between individuals but remains a key challenge for many patients. Compared to apalutamide plus ADT, darolutamide plus ADT is generally better tolerated, particularly in relation to fatigue and preserving cognitive function (based on the findings of the ARASENS/TITAN trials). This is thought to be due to darolutamide's limited ability to cross the blood-brain barrier. Some men may experience intolerance to apalutamide, making darolutamide an important alternative treatment option. Patients with hormone-sensitive metastatic prostate cancer want more treatment options – not only to improve survival but to help balance life expectancy with quality of life. The ability to choose a treatment that fits their lifestyle, health status, and personal preferences is increasingly important to patients and aligns with NHS goals of delivering personalised, patient-centred care.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Darolutamide plus ADT offers patients with mHSPC the hope of living longer with stable disease, by improving progression-free survival and delaying the time to disease progression compared to ADT alone. This means patients may be able to maintain their quality of life for longer. Patients are also likely to value that darolutamide is generally less likely to cause troublesome side effects such as fatigue, confusion, and memory problems – issues that can significantly affect daily life. In addition, darolutamide is associated with a lower risk of falls and fractures, which is particularly important for older patients or those already at higher risk of injury. Another important consideration is that darolutamide has fewer drug interactions than apalutamide, which may make it a better option for patients who take multiple medications or who have other health conditions. Some patients may still prefer apalutamide plus ADT, as some data suggest a slightly higher survival benefit in certain settings. This highlights the importance of having multiple treatment options available to support personalised care and shared decision-making between patients and clinicians.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Some patients may prefer taking all tablets at once as per apalutamide, particularly those with memory problems.

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.	Certain groups of patients may benefit more or less from the technology depending on their individual health concerns. These include: • Older patients or those with a history of cognitive issues: These patients may be particularly concerned about potential cognitive side effects of the technology. • Patients at higher risk for falls and fractures: Those who are more vulnerable to these issues may experience different outcomes with the technology. • Patients with multiple medications or comorbidities: The technology could be beneficial for these patients due to a reduced risk of harmful drug interactions. • Patients concerned about fatigue: The technology may offer a reduction in the severity of fatigue for these individuals. Overall, specific health concerns, such as cognitive health, fall risk, medication interactions, and fatigue, may influence how well certain patients respond to the technology.

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?	No

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Living with hormone-sensitive mHSPC means facing the challenges of both the disease itself and the side effects of its treatment – not only the physical effects, but also the significant emotional and psychological impact. • Darolutamide plus ADT directly addresses several of the most important unmet needs in the treatment of mHSPC – improving survival, delaying disease progression, minimising side effects such as fatigue, and expanding treatment options for patients. • Darolutamide plus ADT offers patients with mHSPC the hope of living longer with stable disease, by improving progression-free survival and delaying the time to disease progression compared to ADT alone. • Compared to apalutamide plus ADT, trial results show that darolutamide plus ADT is generally better tolerated, particularly in relation to fatigue and preserving cognitive function • Certain groups of patients with mHSPC may benefit more or less from the technology depending on their individual health concerns.

Thank you for your time.

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

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Darolutamide with androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer [ID6452]

Patient Organisation Submission

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

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 a voluntary organisation based in London. It is a registered charity in England and Wales (1005541) and in Scotland (SC039332). Registered company number 02653887.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Bayer - £592 (2024, Specialist Nurses Service) Accord - N/A Amdipharm Mercury Company - N/A Astellas Pharma - N/A AstraZeneca - N/A Ferring Pharmaceuticals - N/A Ipsen - N/A Johnson and Johnson Innovative Medicine - N/A Kent Pharma - N/A Mylan - N/A
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. Further evidence from people contacting our specialist nurse service or emailing our support services.

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?	Although prostate cancer affects each patient differently, we know that a diagnosis of metastatic prostate cancer initially causes fear, distress and anxiety for patients and their families. Many patients will live for some years with advanced prostate cancer, but the incurable nature of advanced disease can, for some, be very difficult to manage psychologically. One of the primary ways in which advanced prostate cancer affects the lives of patients is through the symptoms it can cause. It is not possible to be specific about the symptoms for hormone-sensitive metastatic prostate cancer, as there is limited evidence available that is specific to this sub-population of men. As such, here we discuss evidence-based symptoms for advanced prostate cancer. One of the common symptoms is fatigue, which can affect a man's ability to carry out every day self-care tasks and social activities, as well as impacting his concentration, sleep, memory and decision-making. According to a 2024 literature review, cancer-related fatigue affects up to 90% of advanced prostate cancer patients and is often referred to as the most distressing side effect.[1] Bone is the most common site of metastases, and a common symptom of this is bone pain, which affects 75% of symptomatic patients with metastatic prostate cancer.[2] Bone pain can make simple things such as sleeping, walking, and other movement painful and can be debilitating enough to significantly impact the quality of life of these men. If advanced cancer has spread to the bladder or urethra, or the cancer presses on the urethra, it can cause urinary problems, including incontinence, urine retention, blood in the urine and kidney problems. There are also several side effects that are less common but equally impact a man's life day-to-day, such as bowel problems, anaemia, symptoms caused by high levels of calcium in the blood and loss of appetite. A diagnosis of advanced prostate cancer can also significantly impact a man's mental health, particularly as there are no curative treatments for disease at this stage. The emotional burden of the diagnosis is often huge and can result in men experiencing anxiety and/or depression, which can also be exacerbated by fatigue. It is also often emotionally difficult for loved ones of men who have received a diagnosis and can put strain on relationships. Advanced 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.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Men with newly diagnosed metastatic prostate cancer do not have curative treatment options available to them. They (and their carers) will weigh up the quantity of life granted by any treatment with the quality of life during that period including any side-effects or consequences of treatment. Common treatments for men in this indication include androgen deprivation therapy (ADT) alone, or a combination of ADT and chemotherapy (docetaxel). Data from the STAMPEDE trial and CHAARTED study has shown that the addition of docetaxel to ADT provides longer survival for men at this stage of the disease.[3,4] ADT alone can cause a range of adverse effects, including hot flushes, fatigue, sexual dysfunction, and strength and muscle loss. Additionally, hormone therapy is associated with the side effect of bone weakening and fracture.[5] Additional effects from the combination treatment (docetaxel and ADT) include febrile neutropenia (6% of patients), effects on sensory nerves (1%) and effects on motor nerves (1%). Survival is further increased by the addition of darolutamide to docetaxel and ADT (triplet therapy). While the combination of docetaxel and ADT or darolutamide triplet therapy are more effective than ADT alone, many men are contraindicated for chemotherapy, too physically unfit to tolerate it, or would prefer to avoid it. This is illustrated by reports of low levels of uptake of triplet therapy, with inequalities also cited in uptake of docetaxel by ethnicity and men with more comorbidities.[5] Additionally, ADT monotherapy use remains high in Europe,[6] and we have received similar anecdotal evidence from our Specialist Nurses about patients receiving ADT monotherapy. This may suggest that further treatment options with improved effectiveness are needed. Other alternative treatments that don't require chemotherapy include the other androgen receptor pathway inhibitors apalutamide and enzalutamide, which are added to ADT, and show comparable or improved effectiveness to the combination of docetaxel and ADT.[7] These treatments therefore provide additional options to men who are unsuitable for or prefer to avoid chemotherapy. Direct comparisons between these inhibitors (also known as Novel Hormone Therapies or NHTs) are not available from any individual trial, but meta-analysis has demonstrated that the efficacy of these inhibitors, in terms of increasing chance of overall survival, are comparable. These NHTs bring their own profiles of adverse effects, including fatigue, hot flushes and hypertension. We have heard directly from several men that there is a need for more treatments for advanced prostate cancer.

8. Is there an unmet need for patients with this condition?	Existing NHTs give substantial benefits for patient survival over ADT alone and have provided an effective alternative for patients who are contraindicated to or prefer to avoid chemotherapy. However, they bring their own risks of adverse effects, which can severely impact a patient's life day-to-day. There is therefore a strong need for treatments that provide a gentler option. Additionally, increasing the number of effective treatments is critical for patient choice, giving them the option to avoid specific adverse effects. Some patients may already have a restricted pool of these treatments available to them due to existing comorbidities, and there are small subpopulations who may be unsuitable for existing NHTs (e.g. patients suffering from seizures or with an increased seizure risk are unlikely to be suitable for either enzalutamide or apalutamide), so there is a need for further treatment options.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The combination of darolutamide and ADT provides a further effective option to add to the existing treatment pool, giving patients greater choice. The primary benefits of this treatment to patients are the improvements in survival and progression compared to ADT monotherapy that have been observed in clinical trials, combined with the favourable safety profile of darolutamide. A particular advantage of this treatment combination is that it does not include docetaxel, making it suitable for patients unsuitable for or wishing to avoid chemotherapy. The lack of chemotherapy also has practical benefits for patients, such as a lower amount of time spent travelling to and in the hospital receiving treatment. One of the main fears a patient has in this indication is worrying when their prostate cancer may become castration resistant. Patients have said to us that this is the point where they believe that "their cancer is progressing and they will be running out of options". Through the ARANOTE trial, darolutamide doublet therapy has been shown to increase the time until the prostate cancer became castration resistant compared to ADT alone, along with time to PSA progression and the proportion of patients achieving an undetectable PSA level (<0.2 ng/mL).[8] The trial also showed that the combination of darolutamide and ADT improved both overall radiological progression-free survival and risk of death. A caveat to these benefits is that ADT alone is no longer regarded as a preferred treatment option, since the addition of docetaxel and/or NHTs provide further survival benefit. However, as discussed above, ADT monotherapy use remains high in practice. Data directly comparing darolutamide doublet therapy with these preferred treatment options does not exist, but a living systematic review has found that darolutamide is comparably effective with other ARPI combination

	treatments.[9] This treatment would therefore represent another effective choice for patients at this stage of the disease, providing a greater sense of control which can help ease anxiety. The ARANOTE trial also found that adverse effects typically associated with other NHTs (including coronary artery disorders, cardiac arrhythmias, vasodilatation and flushing, bone fracture, mental-impairment disorder, rash, falls, decreased weight, heart failure, cerebral ischemia, diabetes mellitus and hyperglycemia) were low for darolutamide doublet therapy and similar in frequency to in the placebo group.[8] These results suggest that darolutamide doublet therapy may be a safer and more tolerable option than other NHT doublet therapies. This may be linked to darolutamide's low blood-brain barrier permeability.[10] Patients have directly told us that fatigue is a life changing side effect, hindering daily activities which can then impact their family and carers. Notably, in the ARANOTE trial, darolutamide doublet therapy did not increase fatigue compared to ADT alone. This suggests that this treatment could be particularly beneficial for avoiding fatigue. Darolutamide also has a much lower number of drug-drug interactions than enzalutamide and apalutamide, making it potentially a valuable option for patients taking medication for other conditions.[11]

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	As with other NHTs, darolutamide is administered alongside ADT, which brings a range of side effects that impact the lives of patients day to day. These include including hot flushes, fatigue, sexual dysfunction, and strength and muscle loss. The combination of darolutamide and ADT brings its own profile of adverse effects, including increased risk of infection and changes to liver function. However, evidence from its use in patients with castration-resistant prostate cancer indicates that it may be a gentler treatment overall than other NHTs.[12] Patients may wish to avoid specific adverse effects, so the side effects can be taken into account when making treatment decisions, giving patients greater ability to control how treatment could impact their life day-to-day. A recent review found that the magnitude of benefit in median overall survival was lower for darolutamide with ADT than for apalutamide with ADT or abiraterone with ADT (currently under appraisal) when comparing across intention to treat cohorts.[13] This treatment may therefore provide a different balance of efficacy and adverse effects to other NHTs. While fewer drug interactions have been noted for darolutamide than for other NHTs, it does interact with Rosuvastatin, a drug that lowers cholesterol.[15] However, there have not been reports of increased side effects for prostate cancer patients in the non-metastatic castration resistant setting who receive both darolutamide and Rosuvastatin.[15] Additionally, the long-term impact of using darolutamide and ADT as a first line treatment in this setting and on treatment options on disease progression is not defined.

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.	Some patients may already have restricted options in terms of approved NHTs available to them due to existing comorbidities, and there are likely to be patients who are unsuitable for existing NHTs (e.g. patients suffering from seizures or with an increased seizure risk are unlikely to be suitable for either enzalutamide or apalutamide). This combination would expand the treatment options for patients who are unsuitable for chemotherapy, and the tolerability of darolutamide may mean it represents a preferred option for patients with poor bone health or cardiovascular function.[16] Its effectiveness has also been shown in patients with a high Gleason score (≥8), and the treatment was found to be particularly effective in patients with low volume disease, although benefits were observed regardless of disease volume,[17] so these represent patient groups that could especially benefit.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Prostate cancer is a condition that can only affect people with a prostate, and therefore men and others assigned male at birth. Recent work has highlighted that only 39.0% of mHSPC patients in England receive treatment intensification despite level 1 evidence and NICE recommendation. Moreover, inequalities were reported in NHT uptake in this indication across practices in England, for older men, Black men, and men in deprived areas.[5] This underuse of treatment intensification is likely to also represent an issue for this treatment. An additional equity consideration is that this treatment would increase choice for patients with currently unmet needs, including those with more comorbidities, and possibly older men (though the data has not yet been made available for this analysis).

Other issues

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

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• The impact metastatic prostate cancer can have on a patient's life is huge – both in terms of symptoms and the burden of the diagnosis itself. • It is therefore imperative that patients have a greater treatment choice in this indication, giving them some control over how treatment will affect their lives day-to-day. • Darolutamide + ADT represents an effective treatment option that would particularly benefit those unsuitable for current treatment options (including NHTs and chemotherapy). • Like other NHTs, this treatment combination represents an effective option (in terms of survival and progression), but with fewer adverse effects.

Thank you for your time.

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

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

References

1. Cornford, P., Robijn, E., Rogers, E., Wassersug, R. & Fleure, L. Fatigue in Prostate Cancer: A Roundtable Discussion and Thematic Literature Review. *Eur. Urol. Open Sci.* 63, 119–125 (2024).
2. Drudge-Coates, L. *et al.* Recognizing Symptom Burden in Advanced Prostate Cancer: A Global Patient and Caregiver Survey. *Clin. Genitourin. Cancer* 16, e411–e419 (2018).
3. Sweeney, C. J. *et al.* Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. *N. Engl. J. Med.* 373, 737–746 (2015).
4. James, N. D. *et al.* Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet Lond. Engl.* 387, 1163–1177 (2016).
5. Bone problems and osteoporosis in prostate cancer. https://www.cancerresearchuk.org/about-cancer/prostate-cancer/practical-emotional-support/hormone-symptoms/sex-hormones-bone-loss-men.
6. Dodkins, J. *et al.* Does Research from Clinical Trials in Metastatic Hormone-sensitive Prostate Cancer Treatment Translate into Access to Treatments for Patients in the "Real World"? A Systematic Review. *Eur. Urol. Oncol.* 7, 14–24 (2024).
7. Raval, A. D., Chen, S., Littleton, N., Constantinovici, N. & Goebell, P. J. Underutilization of androgen deprivation therapy (ADT) intensification for the treatment of men with metastatic hormone-sensitive prostate cancer (mHSPC): A systematic review of real-world database studies. *J. Clin. Oncol.* 42, 66–66 (2024).
8. Wang, L. *et al.* Comparison of Systemic Treatments for Metastatic Castration-Sensitive Prostate Cancer. *JAMA Oncol.* 7, 412–420 (2021).
9. Saad, F. *et al.* Darolutamide in Combination With Androgen-Deprivation Therapy in Patients With Metastatic Hormone-Sensitive Prostate Cancer From the Phase III ARANOTE Trial. *J. Clin. Oncol.* 42, 4271–4281 (2024).
10. ASCO GU 2025: Choice of Androgen Receptor Pathway Inhibitors (ARPi) by Disease Volume and Timing of Metastases in Metastatic Hormone Sensitive Prostate Cancer (mHSPC). https://www.urotoday.com/conference-highlights/asco-gu-2025/asco-gu-2025-prostate-cancer/158170-asco-gu-2025-choice-of-androgen-receptor-pathway-inhibitors-arpi-by-disease-volume-and-timing-of-metastases-in-metastatic-hormone-sensitive-prostate-cancer-mhspc.html.
11. Wu, X., Han, H., Zhang, C. & Song, W. The Overall Survival and Safety of Men with Metastatic Hormone-Sensitive Prostate Cancer Treated with Combination Therapy of Novel Androgen Receptor Antagonists and Androgen-Deprivation Therapy: A Systematic Review and Meta-Analysis. *J. Oncol.* 2022, 6211059 (2022).
12. Bolek, H. *et al.* Androgen receptor pathway inhibitors and drug–drug interactions in prostate cancer. *ESMO Open* 9, 103736 (2024).
13. Wenzel, M. *et al.* Overall survival and adverse events after treatment with darolutamide vs. apalutamide vs. enzalutamide for high-risk non-metastatic castration-resistant prostate cancer: a systematic review and network meta-analysis. *Prostate Cancer Prostatic Dis.* 25, 139–148 (2022).
14. Azad, A. A. *et al.* Combination Therapies in Locally Advanced and Metastatic Hormone-sensitive Prostate Cancer. *Eur. Urol.* 87, 455–467 (2025).
15. Appukkuttan, S. *et al.* Drug–drug interaction potential among patients with nonmetastatic castration-resistant prostate cancer (nmCRPC) treated with novel androgen receptor inhibitors. *Expert Rev. Anticancer Ther.* 24, 325–333 (2024).
16. Shore, N. *et al.* Evaluation of Clinically Relevant Drug–Drug Interactions and Population Pharmacokinetics of Darolutamide in Patients with Nonmetastatic Castration-Resistant Prostate Cancer: Results of Pre-Specified and Post Hoc Analyses of the Phase III ARAMIS Trial. *Target. Oncol.* 14, 527–539 (2019).
17. Dou, M. *et al.* Based on ARASENS trial: efficacy and safety of darolutamide as an emerging option of endocrinotherapy for metastatic hormone-sensitive prostate cancer—an updated systematic review and network meta-analysis. *J. Cancer Res. Clin. Oncol.* 149, 7017–7027 (2023).
18. Saad, F. *et al.* Darolutamide plus ADT in patients with metastatic hormone-sensitive prostate cancer (mHSPC) by disease volume: Subgroup analysis of the phase 3 ARANOTE trial. *J. Clin. Oncol.* 43, 151–151 (2025).

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Darolutamide with androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer [ID6452]

Patient Organisation Submission

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

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 represent around 120 support groups in England and Wales and through them have several thousand individual members - men and their families whose lives have been affected by prostate cancer. We receive funding from a wide variety of sources including The National Lottery Fund, Movember, Charitable Trusts, Income from individual donations and fund raising events, Prostate Cancer UK, Corporate donations, and income from the pharma industry as either project based grants, payment for services provided by members or unrestricted grants. During tax year 24/ 25 total pharma income contributed 8% of our total income
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment	**YES** Bayer £5,000 Grant Financial support for Annual Conference

companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	£13,800 Grant towards project 'Many Faces' campaign highlighting shared experience of patients Ipsen: £4,850 Grant towards project 'Many Faces' campaign highlighting shared experience of patients Johnson & Johnson: £10,000 Financial support for Annual Conference
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?	Gathering regular input from our members is a priority, and we achieve this through various channels such as at local and national meetings held online as well as in person. Sharing personal experiences of living with PCa is a fundamental function of Tackle. Additionally, we engage in direct communication with individuals and address questions and concerns raised by patients when appropriate. Many of our local groups host local helplines from which we can obtain feedback when required. Our medical advisory board is in place to offer guidance whenever necessary. While the specific treatment currently under evaluation is not yet accessible through the NHS, however there are already combinations of ADT and similar Novel Hormonal Therapies (NHAs) widely used and approved by NICE. Many of our patients are at the stage in their diagnosis and treatment where their cancer is both hormone sensitive and also metastatic. The challenges associated with such treatment are frequently discussed among patients in support groups and on helplines, not only talking about the possible effectiveness of treatment but also focusing on the side effects. Having talked with many such patients over a number of years, I am confident in my ability to comprehend the needs of those patients. Tackle Prostate Cancer support me in stating that it is fitting for me to advocate on their behalf. I have obviously not been able to talk with patients taking Darolutamide for hormone sensitive metastatic PCa but have had contact with patients taking Darolutamide in other clinical conditions –

	particularly in non-metastatic hormone resistant PCa (Biochemical recurrence of PCa). They have given positive feedback concerning efficacy and side effect profile of this drug.

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?	Hormone sensitive metastatic prostate cancer (hsmPca) may develop as a progression from the non-metastatic phase but can also occur in newly diagnosed men. A man newly diagnosed with metastatic hormone sensitive metastatic prostate cancer is given a total 'bombshell' of a diagnosis. Not only is he told he has a cancer but also the possibility that he only has a very limited life span. It is a time of deep emotional and psychological distress for all of these men, their families and carers. This is particularly true for those men who previously had no symptoms and have often been diagnosed on a routine medical examination. A significant number of these men will be relatively young and with young families. The diagnosis will undoubtedly take over the life of the patient not only immediately but often for the whole of the life he has remaining. His future life will be significantly changed by not only the symptoms of his disease but also by the potential side effects of his treatments. He will know he has reduced life expectancy and will need to make plans accordingly. The possibility of extending life and increasing the time before further progression of the disease and the onset of considerable extra problems such as pain from metastases is of paramount importance. Quality of life is a crucial consideration for patients at any stage of their disease. The journey of prostate cancer treatment involves substantial emotional and physical impact for not only patients, but also family members and caregivers. The advantages of 'Doublet' or 'Dual' combination therapy of ADT & NAHs or Chemotherapy have undoubtedly had a great positive influence on all of those people whose lives have been affected by prostate cancer.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Originally treatment of hsmPCa was using monotherapy with Androgen Deprivation Therapy (ADT) alone. Because of the very positive results from Stampede trials involving the use of a combination of ADT and chemotherapy standard of care was rapidly changed to incorporate the combined use of ADT and chemotherapy as initial treatment. This is now regarded as the normal standard of care. Therapy with ADT alone is no longer recommended. Despite evidence supporting combination regimes, recent data from the National Prostate Cancer Audit show that the uptake / use of this adjuvant therapy is not as high as it should be with around 30% patients being potentially undertreated. For those men unable or unwilling to have chemotherapy, or those who experience considerable early side effects from chemotherapy, alternative treatment with NHAs is now approved by NICE. Adding Darolutamide to that group of NHAs will further add to the choice available and enable clinicians to select the most appropriate of those drugs for each individual patient.
8. Is there an unmet need for patients with this condition?	Yes. Whilst most patients will be suitable for similar combination therapies there will be some who are, for various reasons, unable to take any of those currently available. Some patients get early intolerable side effects and need to be given a suitable alternative. Darolutamide could fill that need for that alternative.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The proven efficacy of Darolutamide in other clinical areas makes this a useful alternative here. For many there is the possibility of a better side effect profile. The side effect profile of a drug is obviously important to patients. They require a drug to have the maximum benefit but with the minimum of side effects. The aim of treatment should always be to attain the maximum benefit (i.e. increased quality and quantity of life) for the minimum amount of side effects. Overall, Darolutamide combined with ADT can offer a significant delay in progression of disease with a low treatment burden. In the ARANOTE trial discontinuation rates due to adverse events were less in the Darolutamide group than in the placebo group. The drug was well tolerated. One patient said to me: *"I started taking Darolutamide 4 years ago when my prostate cancer became described as hormone resistant but non-metastatic. I did so with some worries about side effects. But I can honestly say I have had virtually no problems at all. It's all been fine."* And again: *"I am surprised about how safe this drug is. I have had increasing problems with renal failure (related to my previous radiotherapy) and now have around 30% renal function overall. Despite this there have been no problems with the blood tests taken on routine monitoring of my progress."*

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	If a treatment is effective and suitable then patients will accept side effects as long as they are not severe. Dosage regime is easy and acceptable. Treatment does not require regular visits to hospital but most monitoring can be achieved in the community.

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 with any new drug approved by NICE, such approval does not automatically mean it will be made available to all appropriate patients. Integrated Health Boards / local decision makers can decide not to fund a certain drug. NICE have no control over the obvious geographical disparity in availability of treatments.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Whilst not an issue of gender or age equality, when comparing the economics of similar drugs there is a disparity in costs. Currently Darolutamide is not available as a generic drug. However, Enzalutamide and Abiraterone are both available as generic drugs. They should therefore be available to the NHS at a significantly reduced cost to the currently available 'branded' drugs. However, the original appraisals of these drugs by NICE were made using the costings of the branded versions of those drugs at that time. This could potentially bring issues into the process of deciding which of the appropriate drugs available should be used/approved. This needs to be done on a 'level playing field'. Cost issues are always discussed at confidential meetings of the NICE committees and actual costings of drugs to the NHS not made public.

Other issues

13. Are there any other issues that you would like the committee to consider?	In essence, this appraisal would appear to bring Darolutamide into line with other NAHs approved already as combination therapy with ADT. The ARANOTE trial has shown that Darolutamide with ADT significantly improves radiographic progression-free survival, reduces the risk of death, delays the time to the onset of metastatic castration resistant disease and achieved a significant reduction in PSA levels when compared with ADT alone. This is comparable to the finding of trials of other similar NAHs. I am not aware of any studies directly comparing all of these drugs. The incidence of adverse events is acceptable. The drug would appear to be well tolerated by patients. If the costs of the drug are also in a range acceptable and comparable to the other similar drugs, it would seem logical that Darolutamide should be similarly approved by NICE.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Current standard of care of metastatic hormone sensitive prostate cancer is combination therapy and not monotherapy:
	  ○ ADT with chemotherapy
	  ○ ADT with a Novel Hormonal Agent
	• Darolutamide has been shown to be effective as a NAH when used in this context and has a low treatment burden.
	• Darolutamide is well tolerated by patients.
	• Darolutamide is comparable to those NAHs in current usage.
	• It would seem logical to allow Darolutamide to be added to the choice of NAHs available to clinicians when treating patients with metastatic hormone sensitive prostate cancer

Thank you for your time.

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

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

NICE National Institute for Health and Care Excellence

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Darolutamide with androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer [ID6452]

Professional organisation submission

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 the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	Bristish Uro-oncology Group (BUG)
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes or No A specialist in the treatment of people with this condition? Yes or No A specialist in the clinical evidence base for this condition or technology? Yes or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Uro-oncology Group (BUG) is a dedicated professional association for clinical and medical oncologists specialising in the field of uro-oncology. Its overriding aim is to provide a networking and support forum for discussion and exchange of clinical practice, research and policy ideas. BUG is a registered Charity (registration number 1116828) with the overriding aim of "The relief of sickness of persons suffering from urological cancers & the advancement of education for the benefit of the public concerning its identification, diagnosis and treatment". Set up in 2004, the running of the Charity is funded by Membership fees. Its Meetings organisation & provision, solely for Healthcare Professionals, is funded by Delegate registration fees & hands-off grants from Pharmaceutical companies. Any Pharmaceutical support is clearly stated as "having had no input into the programme, selection of speakers, or topics discussed". BUG also runs a website with educational resources and distributes an annual newsletter – both for Healthcare Professionals. BUG's provision of a networking & support forum for discussion & exchange of research & policy ideas ultimately reaps benefits for patients.

5b. 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.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of treatment for patients with mHSPC are improving outcomes (radiological progression free survival, and overall survival) and optimising quality of life.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The main efficacy outcome is a significant reduction in the risk of progression or death with the treatment agents. Other important aspects are reduction of PSA levels, delaying the develpoment of castrate resistant disease, delaying time to pain progression and maintaining the quality of life.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Patients with de novo mHSPC have the choice of enzalutamide, apalutamide as doublet therapies or combination of docetaxel and darolutamide as triplet therapy for treatment intensification, which are all NICE approved. However, the NPCA audit data shows that 60% of mHSPC patients are only receiving hormone therapy (ADT) alone. Hence, there is an unmet need in optimising the treatment for these patients.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Patients with de novo mHSPC have the choice of enzalutamide, apalutamide in combination with ADT as doublet therapies or combination of docetaxel, darolutamide and ADT as triplet therapy for treatment intensification.
9a. Are any clinical guidelines used in the	NCCN, ESMO guidelines and NICE TAs for enzalutamide, apalutamide and docetaxel plus darolutamide.

treatment of the condition, and if so, which?	
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes. The choice of 1st line therapy is dependent on shared decision making keeping in perspective the disease related factors and patient related factors.
9c. What impact would the technology have on the current pathway of care?	The current appraisal will allow another option to be available for patients to choose from. Darolutamide has the advantage of low drug-drug interactions which is an improtant consideration in this group of patients who have other co-morbiditied and are usually on poly-pharmacy.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	If approved, it will be an addition to the treatment options available for patients with mHSPC.
10a. How does healthcare resource use differ between the technology and current care?	It will be no different. The advantage of low drug-drug interactions with Darolutamide may potentially benefit the NHS, with possible reduction in NHS resource use.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	It will be used in secondary care
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment is needed.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Daroluatamide has the advantage of low drug-drug interactions which is an improtant consideration in this group of patients who have other co-morbiditied and are usually on poly-pharmacy. This will allow patients to have more benefit as compared to the current options available.
11a. Do you expect the technology to increase length of life more than current care?	Difficult to say as there are no data of head-to-head comparision between the different agents currently available.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, due to the low risk of side-effects and low drug-drug interactions.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Darolutamide is already approved for use in the nmCRPC setting and in the mHSPC setting in combination with docetaxel (triplet). So, no additional training/ resources are required.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	This option will be discussed in patients who present with spread of cancer outside the prostate. The treatment will be stopped either on progression (on radiology) or significant toxicity. There is no need for any additional testing.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	The QoL benefits would potentially be similar to other options available.
16a. Is the technology a 'step-change' in the management of the condition?	No

16b. Does the use of the technology address any particular unmet need of the patient population?	It will help in optimising treatment intensification in patients with de novo mHSPC.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side-effect profile is very favourable with Daroluamide with low rates of discontinuation of treatment (6%) which is lower than that seen with the placebo in the trial.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, they do.
18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Radiographic Progression free survival, rates of PSA progression, time to castration, and overall survival. These were measured in the ARANOTE trial.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
18d. Are there any adverse effects that were not apparent in clinical	No

trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA712 and TA741]?	No
21. How do data on real-world experience compare with the trial data?	The realworld RECORD (darolutamide in nmCRPC) and RECOMMEND (darolutamie and docetaxel) studies have show ccomparable efficacy outcomes and toxicity in the real word.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	No

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Darolutamide is already in use in the NHS in the nmCRPC setting and in mHSPC setting in combination with Docetaxel. • ARANOTE study shows improvement in radiographic PFS and favourable toxicity profile. • Rates of discontinuation of darolutamide are less than the placebo • Outcomes in the realworld (in nmCRPC and mHSPC in triplet setting) are complarable with the trial data • Darolutamide has low drug drug interactions

Thank you for your time.

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

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Darolutamide with androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer [ID6452]

Professional organisation submission

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 the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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 13 pages.

About you

NICE National Institute for Health and Care Excellence

1. Your name	[redacted]
2. Name of organisation	The Royal College of Pathologists
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Royal College of Pathologists is a professional membership organisation with charitable status concerned with all matters relating to the science and practice of pathology. It is a body of its Fellows, Diplomates, Affiliates and trainees, supported by the staff who are based at the College's London offices. The College is a charity with over 13000 members worldwide. The majority of members are doctors and scientists working in hospitals and universities in the UK. The College oversees the training of pathologists and scientists working in 17 different specialties, which include cellular pathology, haematology, clinical biochemistry and medical microbiology.

5b. 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.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	no
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	no

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Increase survival time rather than provide a cure.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Possibly, if the drug can significantly improve survival for some patients, and particularly for those in whom chemotherapy may be contraindicated.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Androgen deprivation therapy plus docetaxel chemotherapy.
9a. Are any clinical guidelines used in the	NICE

treatment of the condition, and if so, which?	
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes – as per NICE.
9c. What impact would the technology have on the current pathway of care?	Could help those who cannot have chemotherapy, for whatever reason. Could reduce side-effects if used instead of chemotherapy.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Could replace the chemotherapy aspect of current care.
10a. How does healthcare resource use differ between the technology and current care?	The hospital associated costs of chemotherapy would no longer be needed.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
11a. Do you expect the technology to increase length of life more than current care?	
11b. Do you expect the technology to increase health-related quality of life more than current care?	
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Those for whom chemotherapy is contraindicated.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Docetaxel has to be given in hospital, this is a tablet which can be taken at home, so in that way the newer technology is easier.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
16a. Is the technology a 'step-change' in the management of the condition?	

16b. Does the use of the technology address any particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical	

trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA712 and TA741]?	
21. How do data on real-world experience compare with the trial data?	

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Easier than chemo for patients; reduced attendance at hospital. • Potential benefit specifically for those in whom chemotherapy is contraindicated. • The rest of the questions are outside my area of expertise. • •

Thank you for your time.

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

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Darolutamide with androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer [ID6452]

NICE medicines optimisation briefing

January 2025

Key issues

- There are 2 possible comparators, apalutamide and enzalutamide (both with androgen deprivation therapy [ADT]). Apalutamide has an optimised recommendation for use only if docetaxel is not suitable.
- The dose frequency is higher for darolutamide (2 tablets twice a day) compared with apalutamide (1 tablet once a day) and enzalutamide (4 tablets once a day).
- Adverse event profiles (including for falls, fractures, cognitive impairment, and seizures) differ between treatment options. Therefore, the person's risk of these events should be taken into account.

Technology overview

Darolutamide, an oral androgen receptor inhibitor (summary of product characteristics [SPC] for darolutamide) is licensed for use in combination with docetaxel for treating hormone-sensitive metastatic prostate cancer in adults. It is also licensed for treating adults with non-metastatic castration-resistant prostate cancer who are at high risk of developing metastatic disease. It is not currently licensed for treating hormone-sensitive metastatic prostate cancer without docetaxel.

Context

Two other oral androgen receptor inhibitors, enzalutamide (TA712) and apalutamide (TA741), both in combination with ADT, are recommended for hormone-sensitive metastatic prostate cancer in adults. If the cancer is diagnosed at the metastatic stage, the person is considered to have newly diagnosed (de-novo) metastatic hormone-sensitive prostate cancer. A person with non-metastatic hormone-sensitive prostate cancer may also progress to metastatic hormone-sensitive prostate cancer after local therapy (prostatectomy or radiotherapy), where the disease has spread to other parts of the body but is still sensitive to ADT.

Apalutamide in combination with ADT is recommended only if docetaxel is not suitable. Darolutamide with ADT and docetaxel (TA903) has also been recommended by NICE for treating hormone-sensitive metastatic prostate cancer in adults.

Abiraterone, an androgen biosynthesis inhibitor, was assessed by NICE in 2021 (TA721). It was not recommended because, whilst clinically effective, it was not cost-effective. Since publication of the technology appraisal, several generic versions of abiraterone have become available. This TA is being reviewed. The NHS England interim commissioning policy recommends abiraterone and prednisolone as a routine commissioning treatment option within the criteria set out in the policy for newly diagnosed high risk hormone-sensitive metastatic prostate cancer.

The trial for darolutamide with ADT in hormone-sensitive metastatic prostate cancer compares darolutamide in combination with ADT to placebo in combination with ADT in adults (NCT04736199).

NICE has published guidance on the diagnosis and management of prostate cancer (NG131).

Table 1: Characteristics of darolutamide with ADT compared with other treatments for hormone-sensitive metastatic prostate cancer at a similar point in the treatment pathway

	Darolutamide (plus ADT)	Apalutamide (plus ADT)	Enzalutamide (plus ADT)
Mechanism of action	Potent androgen receptor signalling inhibitor that blocks several steps in the androgen receptor signalling pathway. Competitively inhibits androgen binding to androgen receptors.	Potent androgen receptor signalling inhibitor that blocks several steps in the androgen receptor signalling pathway. Competitively inhibits androgen binding to androgen receptors.	Potent androgen receptor signalling inhibitor that blocks several steps in the androgen receptor signalling pathway. Competitively inhibits androgen binding to androgen receptors.
Indication	Darolutamide with ADT is not currently licensed in the UK for the treatment of adult men with metastatic hormone-sensitive prostate cancer. It is only licensed for this indication in combination with ADT and docetaxel (darolutamide SPC).	Apalutamide in combination with ADT is licensed for the treatment of adult men with metastatic hormone-sensitive prostate cancer (apalutamide SPC).	Enzalutamide in combination with ADT is licensed for the treatment of adult men with metastatic hormone-sensitive prostate cancer (enzalutamide SPC).
Technology appraisal recommendation	Not applicable.	Apalutamide plus ADT is recommended as an option for treating hormone-sensitive metastatic prostate cancer in adults, if docetaxel is not suitable (TA741, published October 2021).	Enzalutamide plus ADT is recommended, within its marketing authorisation, as an option for treating hormone-sensitive metastatic prostate cancer in adults. (TA712, published July 2021).

Dosage and route of administration	Two 300 mg oral tablets twice daily (dose from the trial and current licensed indication). Medical castration with a luteinising hormone releasing hormone (LHRH) analogue should be continued during treatment in people who have not had surgical castration.	One 240 mg tablet as an oral single daily dose. Medical castration with a LHRH analogue should be continued during treatment in people who have not had surgical castration.	Four enzalutamide 40 mg oral tablets once a day. Medical castration with a LHRH analogue should be continued during treatment in people who have not had surgical castration.
Resource impact	Oral treatment: convenient, non-invasive. Commercial arrangement in place for TA903 - simple discount patient access scheme.	Oral treatment: convenient, non-invasive. Commercial arrangement in place - simple discount patient access scheme.	Oral treatment: convenient, non-invasive. Commercial arrangement in place - simple patient access scheme.

Current practice

Medicines for treating metastatic prostate cancer are commissioned by NHS England. Usual treatment for hormone-sensitive metastatic prostate cancer always includes ADT, which may be given:

- alone,
- with docetaxel with or without prednisolone,
- with enzalutamide,
- with apalutamide (if docetaxel is not suitable),
- with darolutamide and docetaxel,
- with abiraterone and prednisolone.

Darolutamide with ADT would be another treatment option.

System intelligence from NICE associates indicates that local treatment pathways follow NICE guidance and that darolutamide with ADT would be used at the same place in the treatment pathway as enzalutamide with ADT or apalutamide with ADT or ADT alone. For people with newly diagnosed high-risk hormone-sensitive metastatic prostate cancer, abiraterone with ADT and prednisolone would also be an option.

Patient centred factors

NG131 recommends that docetaxel chemotherapy with ADT should be offered to people with newly diagnosed metastatic prostate cancer who do not have significant comorbidities. NHS England's docetaxel commissioning policy states that docetaxel should not be used in people with a poor overall performance status (World Health Organization performance 3 to 4), pre-existing peripheral neuropathy, poor bone marrow function, or a life-limiting illness. Therefore, darolutamide with ADT, enzalutamide with ADT and apalutamide with ADT, may be preferred options for people who are unable to have docetaxel.

Darolutamide, apalutamide and enzalutamide are all oral treatments and are therefore convenient for the patient. Apalutamide may be preferred because it is taken once a day instead of twice a day and as a single tablet, whereas darolutamide needs to be taken twice a day, as 2 tablets each time and enzalutamide as 4 tablets once a day.

Adverse event profiles (including for falls, fractures, cognitive impairment, and seizures) differ between treatment options. Therefore, the person's risk of these events should be taken into account. Concomitant enzalutamide or apalutamide with coumarin-like anticoagulants should be avoided; therefore, darolutamide may be a preferred option for people taking coumarin-like anticoagulants.

Health inequalities

The choice and treatment options for all patients should take into account a person’s values and preferences along with their clinical conditions and suitability for different treatment options.

Prostate cancer is more common in people of Black African ethnicity, people with a family history of prostate cancer and people with a homologous recombination repair mutation. People of Ashkenazi Jewish ethnicity have a greater risk of having a BRCA gene mutation and so a higher risk of developing prostate cancer (TA951).

As in previous technology appraisals for treating prostate cancer, recommendations should apply to trans women as well as to men.

External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Darolutamide with androgen deprivation therapy for treating hormone sensitive metastatic prostate cancer

---

Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
Authors	Lois Woods, Senior Research Assistant, Evidence Synthesis and Information Specialist Marcia Takahashi, Research Fellow, Health Economics Neelam Kalita, Senior Research Fellow, Health Economics Jonathan Shepherd, Principal Research Fellow, Evidence Synthesis
Correspondence to	Dr Jonathan Shepherd Southampton Health Technology Assessments Centre (SHTAC) School of Healthcare Enterprise and Innovation University of Southampton Alpha House, Enterprise Road, University of Southampton Science Park, Southampton SO16 7NS www.southampton.ac.uk/shtac
Date completed	9th June 2025 (post factual accuracy check version 26th June 2025)
Source of Funding	This report was commissioned by the National Institute for Health and Care Research (NIHR) Evidence Synthesis Programme as project number NIHR175493.

Acknowledgements

We thank the following for providing expert clinical advice to the project team and for reading and commenting on a draft of the report:

Dr Mohini Varughese, Consultant Clinical Oncologist and Honorary Clinical Associate Professor, Department of Oncology, Royal Devon University Healthcare NHS Foundation Trust & Honorary Clinical Associate Professor, University of Exeter

We also thank Geoff Frampton, Principal Research Fellow, Southampton Health Technology Assessments Centre (SHTAC), and Fay Chinnery, Research Fellow, Southampton Health Technology Assessments Centre (SHTAC), for providing a quality assurance review of the draft report.

Declared competing interests of the authors and advisors

The EAG and the clinical advisor declare no competing interests.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Woods, L; Takahashi, M; Kalita, N; and Shepherd, J. Darolutamide with androgen deprivation therapy for treating hormone sensitive metastatic prostate cancer. A Cost-comparison Technology Appraisal. Southampton Health Technology Assessments Centre, 2025.

Contributions of authors

Lois Woods critically appraised the clinical effectiveness systematic review and drafted the report; Marcia Takahashi critically appraised the cost comparison model and drafted the report; Neelam Kalita critically appraised the cost comparison model and drafted the report; Jonathan Shepherd critically appraised the clinical effectiveness systematic review, drafted the report and is the project coordinator.

[redacted]

TABLE OF CONTENTS

LIST OF TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

ADL	Activities of daily living
ADT	Androgen deprivation therapy
AE	Adverse event
AIC	Academic in confidence
AIC	Akaike information criterion
ALT	Alanine aminotransferase
AO	Adverse outcome
APCCC	Advanced Prostate Cancer Consensus Conference
AR	Androgen receptor
ARIs	Androgen receptor inhibitors
ARTA	Androgen receptor-targeted agents
ASI	Androgen synthesis inhibitor
AST	Aspartate aminotransferase
BBB	Blood-brain barrier
BICR	Blinded independent central review
BNF	British National Formulary
BPI-SF	Brief pain inventory – short form
BRMA	Bayesian bivariate random-effects meta-analysis
BSC	Best supportive care
CI	Confidence interval
CIC	Commercial in confidence
CNS	Central nervous system
CPI	Consumer price inflation
CR	Complete response
CrI	Credible interval
CRD	Centre for Reviews and Dissemination
CRPC	Castration resistant prostate cancer
CS	Company submission
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CVD	Cardiovascular disease
CYP	Cytochrome P450
DB	Double blind
DCO	Data cut-off

DDI	Drug-drug interaction
DIC	Deviance information criteria
DOAC	Direct oral anticoagulant
DSU	Decision Support Unit
EAG	External Assessment Group
EAIR	Exposure-adjusted incidence rate
ECOG	Eastern Cooperative Oncology Group
ECOG-PS	Eastern Cooperative Oncology Group Performance Score
eGFR	Glomerular filtration rate
EMC	Electronic Medicines Compendium
EPAR	European Public Assessment Report
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
EQ-VAS	EuroQol Visual Analogue Scale
ESMO	European Society for Medical Oncology
FAS	Full analysis set
FACT-P	Functional Assessment of Cancer Therapy – Prostate
GABAA	γ-aminobutyric acid type A
GnRH	Gonadotropin-releasing hormone
GP	General practitioner
HCP	Healthcare provider
HR	Hazard ratio
HRCU	Healthcare resource use
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IPCW	Inverse probability of censoring weights
IPD	Individual patient level data
IPE	Iterative parameter estimate
IQR	Interquartile range
ITC	Indirect treatment comparison
ITT	Intention to treat

IWRS	Interactive web response system
KM	Kaplan Meier
LHRH	Luteinising hormone-releasing hormone
LYG	Life-year gained
mCRPC	Metastatic castration-resistant prostate cancer
MedDRA	Medical dictionary for regulatory activities
MHRA	Medicines and Healthcare Products Regulatory Agency
mHSPC	Metastatic hormone-sensitive prostate cancer
mITT	Modified intent to treat
mpMRI	Multiparametric magnetic resonance imaging
MRI	Magnetic resonance imaging
NA	Not applicable
NCI	National Cancer Institute
NCI-CTCAE	National cancer institute common terminology criteria for adverse events
NPCA	National Prostate Cancer Audit
NE	Not estimated
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
nmCRPC	Non-metastatic castration-resistant prostate cancer
nmHSPC	Non-metastatic hormone-sensitive prostate cancer
NMA	Network metro analysis
NMB	Net monetary benefit
NCI-CTCAE (v. 5.0)	National Cancer Institute– Common Terminology Criteria for Adverse Events (version 5.0)
NR	Not reported
OATP	Organic anion-transporting polypeptide
OL	Open-label
OLE	Open-label extension
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PC	Prostate cancer
PCWG3	Prostate cancer working group 3
PD	Progressive disease

PFS	Progression-free survival
PFS2	Second progression-free survival
P-gp	P-glycoprotein 1
PRO	Patient reported outcome
PSA	Prostate-specific antigen
PSS	Personal social services
PSSRU	Personal social services research unit
PrSA	Probabilistic sensitivity analysis
PY	Patient years
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RECIST	Response evaluation criteria in solid tumours
RoW	Rest of the world
rPFS	Radiographic/radiological progression-free survival
RPSFT	Rank preserving structural failure time
RR	Relative risk/risk ratio
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
SRE	Skeletal-related events
SSE	Symptomatic skeletal event
SUCRA	Surface under the cumulative ranking curve
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
ToT	Time on treatment
TSD	Technical Support Document
UK	United Kingdom
US	United States
VAT	Value tax added
WTP	Willingness to pay

1 EXECUTIVE SUMMARY

1.1 Summary of the EAG's view of the company's cost-comparison case

Table 1 provides the EAG's bottom line view regarding the validity of the company's case for cost comparison. As can be seen, the EAG considers the criteria have been met, notwithstanding a degree of uncertainty relating to the evidence for similarity of darolutamide to the chosen comparator treatment, apalutamide (this is explained in more detail in this report).

Table 1 Criteria for cost-comparison technology appraisal

Criteria	Criteria met?	EAG considerations
The technology's expected licensed indication is the same as the chosen comparators	Yes	Darolutamide anticipated marketing authorisation is identical to that of the chosen comparator treatment, apalutamide + ADT. Specifically, darolutamide is intended for 'adult men for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy'.
The chosen comparators meet NICE's criteria for cost-comparison	Yes	Doublet therapy with an androgen receptor-targeted agent (ARTA) in combination with androgen deprivation therapy (ADT) is now considered first line standard care in most patients with mHSPC. The two current NICE recommended doublet therapies are apalutamide + ADT and enzalutamide + ADT. The company have chosen apalutamide as their cost comparator, providing an acceptable justification. However, they give little consideration of enzalutamide, and the reasons for or against its potential inclusion as a comparator. Expert clinical opinion to the EAG suggests that both apalutamide and enzalutamide are

Criteria	Criteria met?	EAG considerations
		commonly used as doublet therapy with ADT in practice. The relative market share of the treatments is currently unknown. The EAG considers both doublet therapies are appropriate for cost-comparison. The company is permitted to select just one comparator or more than one comparator.
It is plausible that the technology may incur similar or lower costs compared with the comparators.	Yes	Darolutamide appears to have a better adverse event profile compared to apalutamide, as suggested by the company's indirect treatment comparison (ITC). This is likely to result in reduced resource use and costs for treatment and monitoring. However, we are unable to test this assumption in relation to other cost and resource parameters as the company's economic model is not structured accordingly.

1.2 The decision problem: summary of the EAG's critique

The company's decision problem adheres to the NICE scope, with a couple of exceptions.

Firstly, the population in the NICE scope is 'People with hormone-sensitive metastatic prostate cancer', whereas the decision problem population is 'adult men with mHSPC who are unsuitable for chemotherapy'. The NICE scope does, however, state the relevant comparators as being 'For people in whom docetaxel is not suitable'. The company provide a rationale for darolutamide + ADT positioned as a treatment option in patients who are unsuitable for docetaxel, including the fact that this aligns with NICE guidance for apalutamide + ADT, their chosen cost comparator. The EAG considers the company's proposal for darolutamide in docetaxel ineligible patients is reasonable, though the anticipated marketing authorisation does not restrict the use of darolutamide to a docetaxel ineligible population. The EAG notes that the clinical effectiveness evidence for darolutamide, the ARANOTE trial, did not explicitly define the participants as being docetaxel eligible/ineligible. Rather, the trial appears to include an all-comer population.

Secondly, the decision problem does not include the two subgroups of interest listed in the scope. That is, people with newly diagnosed metastatic prostate cancer and people with high-risk metastatic prostate cancer. The company notes that most patients in the ARANOTE trial (72.5%) had newly identified mHSPC and the clinical outcomes for this subgroup are consistent with the whole trial population. Hence, a subgroup analysis would add little new information. The company also discuss the challenges in defining high risk disease and note the absence of high-risk patients in the ARANOTE trial. Expert clinical advice to the EAG suggests there is variability in practice in how high-risk patients are identified. The EAG agrees with the company's decision to not include the subgroups.

1.3 The clinical effectiveness evidence: summary of the EAG's critique

The company's pivotal phase III trial, ARANOTE, is a multi-centre, double blind study with relevant outcome measures including radiological progression free survival (rPFS) and overall survival (OS). Despite there being no UK participants recruited, the trial can be considered generally representative of the mHSPC population seen in routine NHS practice. The trial did not recruit docetaxel-ineligible patients though prior prostate cancer treatment with docetaxel or immunotherapy was not permitted.

The ARANOTE trial demonstrated statistically superior efficacy of darolutamide + ADT compared to placebo + ADT at the primary completion analysis, triggering unblinding of the trial and patient crossover from the placebo + ADT arm into the darolutamide + ADT arm. The effect of crossover is potential confounding of the differences in OS between the trial arms at the final analysis. The overall survival (OS) analyses were adjusted for crossover in sensitivity analyses and the results were consistent with the ITT analysis. However, the OS data remains immature with few events and must be interpreted with caution.

The company conducted an indirect treatment comparison (ITC) to compare the relative efficacy of darolutamide + ADT versus apalutamide + ADT. Standard methods were used to construct the NMAs and were clearly reported. The ITC results showed a trend towards favouring apalutamide + ADT for rPFS and OS, and a trend favouring darolutamide for quality of life and adverse events. Only in the comp any base case did results show any statistically significant differences: for time to deterioration in the Functional Assessment of Cancer Therapy – Prostate (FACT-P) score and for discontinuation due to adverse events; but as these differences are in favour of darolutamide + ADT a cost-comparison analysis remains appropriate.

1.4 The cost-comparison evidence: summary of the EAG's critique

The company provided a cost comparison model that estimated only the difference in the drug acquisition costs between the darolutamide + ADT and apalutamide + ADT. The EAG were unable to test the impact of varying the parameter inputs, such as resource use, subsequent treatments, and adverse events on the overall cost-comparison results, as they were not included in the model and the CS. However, based on the clinical evidence and the clinical advice to the EAG, darolutamide + ADT is likely to have similar efficacy, similar use of resources and costs (see sections 5.1 and 5.2) to apalutamide + ADT. Therefore, we do not expect that the inclusion of these parameters would impact the results negatively.

The company's base case results suggest that darolutamide + ADT is associated [redacted] relative to apalutamide + ADT, with an incremental cost of [redacted] The EAG included a half-cycle correction to the company's model (see section 5.3 and 6.3), and the corrected results slightly decreased to [redacted] (see Table 2 below). A PAS discount for darolutamide is applied, and apalutamide and ADTs (leuprorelin, goserelin, and triptorelin) are costed at list prices. Results with price discounts for apalutamide and ADTs are reported in a separate confidential addendum.

Table 2 EAG correction to the company base case: PAS price for darolutamide and list price for apalutamide and ADT medications

	Darolutamide + ADT	Apalutamide + ADT	Difference
Company base case	[redacted]	£146,218	[redacted]
+ half-cycle correction	[redacted]	£145,022	[redacted]
EAG correction to the company base case	[redacted]	£145,022	[redacted]

Source: EAG corrected cost comparison model
PAS, Patient access scheme; ADT, Androgen deprivation therapy

We performed a range of EAG exploratory scenarios and presented them with the company scenarios in section 6.4 Table 10 using the EAG corrected cost comparison model. The scenarios that have the most significant effect on the incremental cost results are:

- Changing the ToT distribution curve distributions varied the incremental total cost from [redacted] (base case: log-logistic) to [redacted] (Gompertz distribution).
- Considering rPFS as the drug cost adjustment-based curve and testing different distributions varied the incremental total cost from [redacted] (generalised gamma distribution) to [redacted] (Gompertz distribution).

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to NICE from Bayer on darolutamide with androgen deprivation therapy (ADT) for treating hormone sensitive metastatic prostate cancer (mHSPC). It identifies the strengths and weakness of the CS. A clinical expert was consulted to advise the external assessment group (EAG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the EAG via NICE on 13th May 2025. A response from the company via NICE was received by the EAG on 28th May 2025 and this can be seen in the NICE committee papers for this appraisal.

2.2 Background

The company proposes darolutamide in combination with androgen deprivation therapy as a treatment option for people with metastatic hormone sensitive prostate cancer (mHSPC) who are unsuitable to receive docetaxel. The company considers darolutamide is more tolerable and associated with fewer adverse effects compared to current NICE recommended standard of care, apalutamide + ADT, and enzalutamide + ADT. For this reason, they consider a cost- comparison technology appraisal to be appropriate. In the following sub-sections the EAG summarises and critiques the background information on this topic presented in the company submission (CS).

2.2.1 Background information on hormone sensitive metastatic prostate cancer.

The CS gives a detailed description of prostate cancer, in terms of its incidence and prevalence, risk factors, natural history, symptoms, prognosis and socio-economic consequences. The CS notes key risk factors for prostate cancer including age, prostate-specific antigen (PSA) level, obesity, a family history of prostate cancer, and ethnicity. Notably, Black African males are at significantly higher risk than White or Asian males.

2.2.2 Background information on darolutamide with androgen deprivation therapy

Darolutamide is a non-steroidal androgen receptor inhibitor for the treatment of prostate cancer. It belongs to a group of drugs known as ARTAs (androgen receptor targeted agents). First generation ARTAs include bicalutamide, flutamide, and nilutamide. These drugs work by competitively blocking the androgen receptor. The second generation ARTAs, such as abiraterone, enzalutamide and apalutamide, differ by inhibiting the androgen receptor, preventing it from binding to androgens and promoting cancer cell growth.

The CS notes that although darolutamide has the same mechanism of action as other second generation ARTAs it is a "more polar molecule, with a flexible structure, and hydrogen bond-forming potential" (CS page 12). The CS explains that "the distinct chemical structure of darolutamide differentiates it from apalutamide and enzalutamide, and results in reduced blood-brain barrier penetration and low central nervous system side effects" (CS page 26). The EAG's clinical expert commented that currently available ARTAs such as apalutamide and enzalutamide are chemically very similar, and that darolutamide shares some similarities but structurally is slightly different with the additional advantage of low penetration of the blood brain barrier. The expert echoed the company's assertion of fewer central nervous system adverse events from darolutamide, though the expert also pointed out that some events, such as seizures, are uncommon. For example, they estimated that only one of their patients has reported a seizure in the last five years.

Darolutamide is currently recommended by NICE for two prostate cancer indications, in two prostate cancer sub-populations respectively:

- **Darolutamide in combination with ADT** for treating hormone-relapsed prostate cancer in adults at high risk of developing metastatic disease (NICE TA660). Hormone-relapsed prostate cancer is also referred to as hormone-resistant or castration-resistant cancer and occurs when the patient loses hormone sensitivity. They no longer respond to ADT and their cancer progresses further.
- **Darolutamide in combination with docetaxel and ADT** as a treatment for mHSPC (NICE TA903). This is the same population group included in the NICE scope for this current NICE appraisal. These patients are still responsive to hormone therapy but have already progressed to the metastatic stage of the disease, with some patients presenting with *de novo* metastases.

2.2.3 The position of darolutamide with androgen deprivation therapy in the treatment pathway

The CS describes the current care pathway with reference to clinical guidelines from NICE, European Society of Medical Oncology (ESMO) and the European Association of Urology, plus advice from the company's expert advisory board. In terms of initial treatment for mHSPC the CS notes the following:

- **Current ESMO guidelines recommend triplet or doublet therapy as first line treatment for mHSPC.** The CS estimates that most patients in England and Wales with mHSPC (around 70 – 80%) begin treatment with ARTA + ADT doublet therapy,

and around 10-20% of patients receive ARTA + ADT + chemotherapy triplet therapy. The current NICE recommended doublet therapies are apalutamide + ADT, and enzalutamide + ADT. The only triplet therapy currently recommended by NICE is darolutamide + docetaxel + ADT. The EAG's clinical expert commented that doublet therapy is beneficial for most patients and the minimum standard of care is to consider at least doublet therapy for patients who are fit enough. The expert explained that triplet therapy (a 'stronger' regimen due to the inclusion of chemotherapy) would be considered the preferred option in patients who have poor prognostic features at diagnosis who may not respond adequately to doublet therapy. Typically, these would be patients with high volume disease, or visceral metastasis. The expert commented that the decision to give triplet therapy can be influenced by the patient's pathology, for example if they have a Gleason primary pattern 5 cancer. This is the highest grade in the Gleason grading system for prostate cancer, indicating the most aggressive and poorly differentiated cancer cells. The company's experts advised that if a patient is fit enough to receive chemotherapy, they would be offered triplet therapy.

- The CS, in the EAG's interpretation, appears to suggest that triplet therapy is the preferred standard of care in mHSPC and would be given to all patients who can tolerate, and are willing to undergo, chemotherapy. The EAG's clinical expert had a slightly different view, commenting that in her experience triplet therapy tends to be targeted to patients with a disease pattern that demonstrates poorer prognosis features at diagnosis. Another consideration mentioned by the clinical expert is that if first line treatment includes docetaxel it is unlikely that docetaxel would be given as a subsequent treatment when the cancer progresses. Some patients prefer to begin their treatment with an ARTA + ADT regimen, and reserve docetaxel as a possible future treatment option when their ARTA treatment response attenuates (assuming they will still be able to tolerate chemotherapy later on).
- **The company proposes darolutamide + ADT as a first line treatment option in mHSPC, specifically for patients ineligible for docetaxel.** The CS notes that some patients are unable or unwilling to tolerate the cytotoxic effects of docetaxel chemotherapy. The docetaxel-ineligible patient population has been considered in previous NICE technology appraisals, namely TA741 (apalutamide plus ADT in mHSPC), TA412 (Radium-223 dichloride in mCRPC), and in an NHS England Clinical Commissioning Policy Statement (in mHSPC).[1] In essence, suitability for docetaxel is made on an individual patient basis informed by a risk-benefit assessment of various patient factors.

- We discuss the company's proposed restriction in their decision problem to docetaxel ineligible patients (see section 3). The CS suggests that there is current unmet need for a non-chemotherapy doublet treatment regimen in mHSPC. Although apalutamide + ADT and enzalutamide + ADT are established agents which can be used in patients who are deemed unsuitable for docetaxel, the company argues that they are associated with significant treatment-related toxicities (e.g. central nervous system adverse effects, fatigue, hypertension, seizures, skin toxicity) and drug-drug interactions. Darolutamide, in contrast, is claimed to have a more favourable tolerability profile and is less likely to interact with other medications including those used to treat common comorbidities (e.g. cardiovascular disease). The company provides a detailed justification in support of their view, citing their expert advisory board, clinical trial data and an APCCC consensus opinion. The EAG's clinical expert is of the opinion that there isn't necessarily unmet need in mHSPC but acknowledged that enzalutamide and apalutamide are associated with certain adverse effects, notably fatigue, central nervous system effects (e.g. seizures, risk of falls) and rash. In her experience apalutamide tends to cause more adverse effects and consequently it is given less often compared to enzalutamide. Darolutamide, based on her clinical experience of prescribing triplet therapy, is well tolerated.

EAG comment on the background information

The CS provides detailed and comprehensive background information on mHSPC, the current care pathway, and the proposed use of darolutamide + ADT as an initial treatment option for patients unsuitable for docetaxel in the metastatic disease setting. The EAG's clinical expert generally agreed with the company's description of the current care pathway though noted likely variation in clinical practice. The company suggests that darolutamide + ADT offers potential advantages over currently used ARTA + ADT treatments, including better tolerability and fewer adverse effects. The EAG's clinical expert advisor concurs with this, based on clinical experience of treating patients with darolutamide triplet therapy. These advantages are attributed to the distinct chemical structure of darolutamide. The EAG's view is that despite its novel features, darolutamide can be regarded as sufficiently similar in mechanism of action to the current NICE recommended ARTAs for mHSPC (i.e. apalutamide + ADT and enzalutamide + ADT). This is one of the factors necessary to support the case for a cost-comparison rather than a cost-utility technology appraisal.

3 CRITIQUE OF THE COMPANY'S DEFINITION OF THE DECISION PROBLEM

Table 3 below summarises the decision problem addressed by the company in the CS in relation to the final scope issued by NICE and the EAG's comments on this. Overall, the company's decision problem matches the NICE scope, with a couple of exceptions:

- **Population: docetaxel-ineligible.** The company specify a docetaxel-ineligible population in their decision problem, whereas the population in the NICE scope is broader (all people with mHSPC) which aligns with the indication in the draft Summary of Product Characteristics (SmPC)[2] for darolutamide. However, the comparators in the NICE scope are described as "for people in whom docetaxel is not suitable" which implies that a docetaxel-ineligible population is relevant to this appraisal. The EAG do not view this as a decision problem issue.
- **Subgroups: none**. The company chose not to assess darolutamide + ADT in the two subgroups in the NICE scope: patients with de novo (newly diagnosed) metastatic disease and patients with high-risk disease. We find that the rationale for the similarity of results of the de novo group compared to the ITT population would be better backed up with data, however the other justifications are appropriate (see Table 3 below).

Table 3 Summary of the decision problem

	Final scope issued by NICE	Company's decision problem and rationale if different from the final NICE scope	EAG comments
Population	People with hormone-sensitive metastatic prostate cancer	Adult men with mHSPC who are unsuitable for chemotherapy.	The NICE scope matches the proposed licensed indication for darolutamide + ADT which is treatment of adult men with mHSPC (draft SmPC 4.1). The company's decision problem restricts the population to adult men with mHSPC who are unsuitable for chemotherapy, i.e. docetaxel-ineligible. The company states that this population aligns with the chosen cost-comparator, apalutamide + ADT, which NICE recommends as an option for mHSPC in patients who are unsuitable for docetaxel (CS section B.1.1) and the EAG agrees that this is appropriate. As this population aligns with the definition of the comparators in the NICE scope, as treatments for people in whom docetaxel is not eligible, there is no issue.
Intervention	Darolutamide with androgen deprivation therapy	Darolutamide with androgen deprivation therapy.	As per scope; no comment.
Comparators	For people in whom docetaxel is not suitable:	Apalutamide with androgen deprivation therapy.	The choice of apalutamide + ADT as the comparator is in accordance with the NICE criteria for cost comparisons. Enzalutamide + ADT also meets the NICE criteria for cost

	Final scope issued by NICE	Company's decision problem and rationale if different from the final NICE scope	EAG comments
	• Apalutamide and androgen deprivation therapy • Enzalutamide and androgen deprivation therapy	As this submission is a cost comparison, we have compared darolutamide with a single NICE-recommended comparator, apalutamide. NICE technology appraisal 741 recommends apalutamide at the same point in the treatment pathway with the same wording as is anticipated for darolutamide. That is, apalutamide is recommended for people with mHSPC who are unsuitable for chemotherapy.	comparisons. The rationale provided by the company is that enzalutamide is not used in the same docetaxel ineligible population as proposed for darolutamide + ADT (clarification response A1), although the NICE TA712 recommendation states that enzalutamide + ADT offers another option for people who cannot have docetaxel.[3] In the EAG's view, either comparator would be appropriate for the population in the NICE scope and in the indicated population in the SmPC. The company is permitted to include just one cost comparator treatment, or more than one if preferred.
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rate • Time to hormone relapsed prostate cancer	The outcome measures to be considered include: • Overall survival • Radiographic progression free survival • Time to castration resistant prostate cancer • Time to subsequent therapy • Prostate-specific antigen undetectable rate • Time to prostate-specific antigen progression	The company decision problem includes all outcomes in the scope except response rate for which the company justification is appropriate.

	Final scope issued by NICE	Company's decision problem and rationale if different from the final NICE scope	EAG comments
	• Time to subsequent treatment • Prostate-specific antigen undetectable rate • Time to prostate-specific antigen progression • Time to pain progression • Adverse effects of treatment • Health-related quality of life.	• Time to pain progression • Adverse effects of treatment • Health-related quality of life. • **Radiographic progression free survival (rPFS)** was the primary endpoint in the ARANOTE study. • **Response rate** was not a pre-planned endpoint in the ARANOTE study and thus these data will not be included in this submission. Response rate is not generally used as an outcome measure in advanced prostate cancer, as prostate metastases, particularly bone metastases, generally do not show radiological responses to treatment, even though overall the treatment may be working.	
Economic analysis	The NICE reference case stipulations for expressing cost-effectiveness in ICERs, cost-comparisons, time horizon, cost	Cost-comparison model considered from an NHS perspective.	The company provided a simple cost-comparison analysis that evaluates the difference between the drug acquisition costs of darolutamide + ADT and apalutamide + ADT. The company assume that everything else, mortality, administration costs, resource use, adverse events, etc., are the same.

	Final scope issued by NICE	Company's decision problem and rationale if different from the final NICE scope	EAG comments
	considerations, commercial arrangements, and availability of biosimilars, etc., should be taken into account. [Abridged version of the text in CS Table 1.]		There is no function available in the cost-comparison spreadsheet to verify or explore differing parameters (clarification question B1). The cost-comparison uses a lifetime horizon, and the costs are considered from an NHS and PSS perspective, which are both appropriate. Further details are in section
Subgroups	If the evidence allows, the following subgroups of people will be considered: • people with newly diagnosed metastatic prostate cancer • people with high-risk metastatic prostate cancer	No subgroups. **Adult men with newly diagnosed metastatic prostate cancer** Both patients with M1 (de novo) and M0 (recurrent) at initial diagnosis have been included in ARANOTE. The majority of patients (72.5%) were de novo and the results in ARANOTE have been consistent across these subgroups. Therefore, the appraisal has focused on the ITT population. Consistency between these subgroups gives further re-assurance that darolutamide is similarly efficacious in both	No subgroups. De novo disease is reported in the ARANOTE pivotal trial as a baseline characteristic (metastases at initial diagnosis: de novo/recurrent/unknown; CS Table 8) and de novo participants comprise the majority (72.5%). It is not possible for the EAG to verify whether their results are consistent with the ITT population because they are not included in the results of the pre-specified subgroup analyses (CS Figure 10). Results from all the other pre-specified subgroup analyses are consistent with the results from the ITT analyses, however it would have

	Final scope issued by NICE	Company's decision problem and rationale if different from the final NICE scope	EAG comments
		newly diagnosed de novo patients and patients with mHSPC in general. **Adult men with high-risk metastatic prostate cancer** It is not clear what the high-risk metastatic prostate cancer definition is in the scope. ARANOTE has been stratified by extent of disease (i.e. non-regional lymph node metastasis, bone metastasis, and visceral metastasis). The efficacy observed in ARANOTE was consistent across these three subgroups. There was no classification by 'high-risk' disease in ARANOTE. There is inconsistent use of 'newly diagnosed' and 'high risk' for randomisation across all mHSPC trials. Furthermore, although appraisals for apalutamide in mHSPC also listed these subgroups in their scopes they were never explored by the submitting company nor was the lack of data in these subgroups highlighted as a key issue during the	been useful for the company to present the de novo group alongside these to verify their statement. We find that high-risk mHSPC is difficult to define. Our clinical expert advised that definitions of high-risk differ between metastatic and non-metastatic disease. For metastatic disease risk is based on extent of bone metastases or presence of visceral metastases. In non-metastatic disease high risk is based on the Cambridge prognostic score. There is no specific subgroup in the pivotal ARANOTE trial that represents 'high-risk' mHSPC. The pre-specified subgroups in the ARANOTE trial cover various markers of high-risk, e.g. high-volume disease, presence of visceral metastases, high Gleason score ([redacted]8), but are not definitions of high-risk disease in themselves. Results for these individual subgroups, however, were also generally consistent with the results of the ITT population.

	Final scope issued by NICE	Company's decision problem and rationale if different from the final NICE scope	EAG comments
		appraisal. As such, this appraisal has focused on the ITT population.	
Special considerations including issues related to equity or equality		[The company considers the following: • patients with a history of seizures • patients with multiple comorbidities at risk of drug-drug interactions (DDIs)] • [Rationale is in the full text of the company decision problem in CS Table 1.]	**Patients with a history of seizures.** Darolutamide is unique among ARTAs in that it does not cross the blood brain barrier (see also section 2.2.2). This is a small patient group (ARANOTE pivotal trial n=1; ARASENS trial n=6; EAG's clinical expert has seen 1 patient (on enzalutamide) with seizures in the last 5 years) that would benefit from the addition of darolutamide + ADT as a treatment option. **Patients with multiple comorbidities.** The number of DDIs associated with darolutamide are significantly fewer than for other ARTAs.[4-6] The availability of treatment with darolutamide may improve ease of medication management for mHSPC patients who are frequently already receiving multiple drugs.

Source: Reproduced from CS Table 1 with some abridgement, and additional EAG comments.
Abbreviations: ADT, androgen deprivation therapy; ARTAs, androgen receptor targeted agents; DDIs, drug-drug interactions; ICERs, incremental cost-effectiveness ratios; ITT, intention to treat; mHSPC, metastatic hormone sensitive prostate cancer; rPFS, radiographic progression free survival.

EAG comment on the company's decision problem

The company's decision problem is similar to the NICE scope for this technology appraisal, with the main difference being company's decision not to assess cost comparison for the de novo (newly diagnosed) and high-risk patient subgroups in the NICE scope. The EAG notes that the other current NICE recommended treatment for patients with mHSPC, enzalutamide + ADT, is also used to treat patients unsuitable for docetaxel. The company favoured apalutamide + ADT as their chosen cost comparator treatment, but did not explicitly state whether enzalutamide + ADT would also be an appropriate comparator. The company is permitted to select just one NICE recommended treatment for comparison with darolutamide + ADT, but also has the option of comparing against more than one recommended treatment.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

The company conducted a systematic literature review (SLR) to identify randomised controlled trials and real-world evidence of the clinical effectiveness of treatments for mHSPC (CS Appendix D). An SLR for studies reporting cost and healthcare resource use for mHSPC was also conducted (CS Appendix G); but is not referred to in the main submission document.

The clinical effectiveness SLR methods are mostly adequate (a summary of the EAG's appraisal is in Appendix 1). The clinical effectiveness SLR included 42 studies overall (CS Appendix Table 15). Relevant to this appraisal, the company identified one RCT that evaluated darolutamide + ADT compared to placebo + ADT in mHSPC: the pivotal phase III ARANOTE trial[7] which is discussed in section 4.2 below, and one RCT that evaluated apalutamide + ADT compared to placebo + ADT in mHSPC: the phase III TITAN trial,[8] discussed in section 4.3 below.

EAG comment on the review methods

Minor aspects of reporting the methods are missing from the CS, and the company may not have provided the correct excluded studies list, but on investigation we found that no relevant studies with results have been omitted. We agree that ARANOTE and TITAN are the included studies that provide the most relevant results for this appraisal.

4.2 Critique of the ARANOTE trial

The ARANOTE trial is a company-sponsored international phase III randomised placebo-controlled trial evaluating the clinical efficacy and safety of darolutamide + ADT vs placebo + ADT.[7]

4.2.1 ARANOTE study design

Table 4 below summarises the ARANOTE trial study design.

Table 4 Overview of the ARANOTE trial

Study characteristic	Details
Study design	RCT. Randomised intervention: placebo 2:1; stratified according to presence of visceral metastases and use of prior local therapy. Double blind until primary completion analysis; open label thereafter.

Study characteristic	Details
Location	133 sites in 15 countries across Europe, Asia, Australia and the Americas. No UK sites or patients.
Population	Men with mHSPC, including both de novo disease, i.e. metastatic at diagnosis, (72.5%) and recurrent disease (approximately 21%).
Pre-specified subgroups	Age (<65/65-74/75-84/≥85), PSA (<median/≥median), ECOG PS (0/≥1), Gleason score (<8/≥8), disease volume (high/low), race (White/Asian/Black/other), Region (Europe and rest of the world/Asia/Latin America), Visceral metastases (yes/no), prior local therapy (yes/no).
Key eligibility criteria	• Confirmed metastatic adenocarcinoma of the prostate • ECOG PS of 0, 1 or 2 • Started ADT ≤12 weeks before randomisation • Adequate bone marrow, liver and renal function • Prior chemotherapy (docetaxel or immunotherapy) for prostate cancer was not permitted.
Intervention	Darolutamide (600 mg BID) + ADT (n=446)
Comparator	Placebo (darolutamide matched tablets BID) + ADT (n=223) NB in practice this represents ADT monotherapy which is no longer standard of care in the NHS (see section 2.2.3).
Primary outcome	**Radiological progression free survival (rPFS**) (see section 4.2.4 and 4.2.5.1)
Secondary outcomes	**OS** (see section 4.2.4 to 4.2.5.2) Time to initiation of subsequent cancer therapy Time to CRPC Time to PSA progression PSA undetectable rate Time to pain progression **Adverse events** (see section 4.2.4 and 4.2.6)
Other outcomes	PFS2 (investigator-assessed) Time to symptomatic skeletal event **Time to deterioration in FACT-P total score** (see section 4.2.4) Time to first prostate cancer-related invasive procedure
Crossover	• [redacted] participants who were still on study treatment in the placebo + ADT arm crossed over to open label darolutamide + ADT after the primary completion analysis (board approved, due to ethical reasons). • RPSFT and IPE statistical methods (pre-specified in the SAP) were used to adjust for treatment switching in sensitivity analyses of OS (see section 4.2.4).
Duration of study	After a 28-day screening period, participants commenced treatment with the study drug and were assessed in clinic every 12 weeks for 12

Study characteristic	Details
	± 1 months. Thereafter, participants were contacted every 12 weeks until death, loss to follow-up, withdrawal of consent or end-of-study.
Main analyses	**Primary completion analysis:** assessed primary outcome of rPFS and all other outcomes; median follow-up: 25.3 months and 25.0 months for darolutamide + ADT and placebo + ADT respectively; database lock June 2024. **Final OS analysis:** assessed OS and safety; median follow-up: [redacted] according to original assignment to darolutamide + ADT and placebo + ADT arms respectively; database cut-off [redacted]

Source: CS section B.3.3.1; CS Figure 10; CS Tables 7 and 8; Saad 2024[7]; Final OS Results Summary[9].
Abbreviations: ADT, androgen deprivation therapy; BID, bis in die [twice a day]; CRPC, castration-resistant prostate cancer; EAG, evidence assessment group; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IPE, iterative parameter estimate; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival; PFS, progression free survival; PSA, prostate-specific antigen; RCT, randomised controlled trial; rPFS, radiographic progression free survival; RPSFT, rank preserving structural failure time; SAP, statistical analysis plan; UK, United Kingdom.
Outcomes in **bold font** are used in the company's indirect treatment comparison (CS section B.3.9.3; section 4.3 of this report).

EAG comment on the ARANOTE trial design

The ARANOTE study is a generally well-designed RCT. The EAG doesn't have any major concerns about the study or its appropriateness to inform this NICE technology appraisal.

4.2.2 ARANOTE population baseline characteristics

Participant demographic and clinical characteristics at baseline are reported in CS Table 8. We agree with the company assessment of the baseline characteristics of participants in the ARANOTE trial. All characteristics are well balanced between arms, and therefore any reported prognostic factors are well balanced too.

The company note the presence of more advanced disease than the general mHSPC population in this trial due to large proportions of participants with high Gleason scores, de novo disease, and high-volume disease (CS section B.3.3.2). The EAG's clinical expert also advised that the proportion of participants with visceral metastases was high at 12% (CS Table 8) compared to less than 5% in her clinical practice. However, the proportions of patients with these characteristics were balanced between arms and would not bias the trial results.

There are no UK participants in the ARANOTE trial, but our clinical expert confirmed that the baseline characteristics (apart from the high presence of visceral metastases) for the trial population are generally representative of the overall NHS mHSPC population in England and noted that the proportions of Asian and Black participants were representative for a trial. Our expert also noted the low median prostate specific antigen (PSA), approximately 21 ng/mL, whereas she might expect to see approximately 40 ng/mL in practice, however the overall range for serum PSA is wide which is representative.

The ARANOTE trial had broad eligibility criteria (CS section B.3.3.1) and did not prospectively recruit docetaxel-ineligible participants, although prior chemotherapy for prostate cancer was an exclusion criterion. Our clinical expert advised us that there is no strict definition of docetaxel ineligibility and that clinicians make a risk-benefit consideration for chemotherapy for each patient in practice, considering performance status, presence of peripheral neuropathy, diabetes and severity of cardiovascular disease. The baseline characteristics show that most of the participants had an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1 compared to only 3-4% with an ECOG score of 2, and none with a score of 3 or 4 (according to trial eligibility criteria), which alongside inclusion criteria of adequate bone marrow, liver and renal function (CS Table 7) suggests a reasonably fit population.

In addition, the company note in clarification response A9 that the subgroup analysis results for age and ECOG performance status are consistent with the overall trial results. They state that over 91% of participants had at least one comorbidity upon study entry and that the most common comorbidities were vascular disorders, musculoskeletal and connective tissue disorders, renal and urinary disorders and metabolism and nutrition disorders. There is no data from ARANOTE on whether the participants would have chosen not to receive docetaxel if offered (which is the other apalutamide Blueteq criterion for docetaxel-ineligibility). However, the EAG considers that patients who choose not to receive docetaxel for any reason are likely to be representative of the general mHSPC population. On balance, it is likely that the population in the ARANOTE trial is appropriate to represent a docetaxel-ineligible mHSPC population but equally also includes patients suitable for docetaxel.

EAG comment on participant baseline characteristics

4.2.3 ARANOTE risk of bias assessment

The company used the “NICE checklist for RCTs” (which the EAG recognises as the criteria for appraising RCTs devised by the Centre of Reviews and Dissemination (CRD) for

systematic reviews), to judge the methodological quality of the trial. In their judgment the ARANOTE trial is at low risk of bias (CS section B.3.5 and CS Table 11).

The EAG appraised the study using the same checklist (see Appendix 2 of this report). For most of the questions our response agrees with that of the company – that the study is at low risk of bias. However, we introduced a distinction between risk of bias in the randomised double-blind phase and in the open label follow up study period. This distinction was applied to two questions where the risk of bias potentially changes over the course of a study.

For the question 'Were the care providers, participants and outcome assessors blind to treatment allocation? 'we answered 'yes' (low risk of bias) for the primary outcome rPFS. This outcome was assessed only at the primary completion analysis of the double-blinded phase and was prior to study unblinding and the option to crossover from placebo to darolutamide. Blinded independent central review (BICR) used to assess rPFS according to standardised measures RECIST v1.1 and PCWG3 criteria of rPFS is a further justification for our judgment.

Outcomes reported after the primary completion analysis, that is, final OS and final adverse events we regard as at high risk of bias. This is due to the effects of unblinding (performance bias) and from patients subsequently crossing over from placebo + ADT arm to the darolutamide + ADT arm. We do, however, acknowledge the company's view that the impact of crossover on OS can be considered reduced given that:

- the period of crossover for the final OS analysis was [redacted], and
- of the [redacted] randomised placebo patients still on study treatment who crossed over to darolutamide after primary completion, only [redacted] died under the darolutamide crossover period (to put this into context, there were [redacted] deaths reported in the final OS analysis after primary completion ([redacted] in the darolutamide arm, [redacted] in the placebo arm)).

EAG comment on risk of bias

The pine characteristics are well balanced between trial arms, and are generally representative of the overall mHSPC population in the NHS. The ARANOTE trial did not specifically recruit docetaxel-ineligible participants, however the trial results are likely generalisable across the mHSPC patient spectrum.

Primary outcome of rPFS, and outcomes assessed at the primary completion analysis, are at low risk of bias, however OS and adverse event outcomes that

were assessed after the primary completion analysis (clarification response A3) are at high risk of performance bias and unclear risk of attrition bias.

4.2.4 Outcomes assessment

The ARANOTE trial outcomes incorporated into the cost comparison model are time on treatment and rPFS (from the darolutamide + ADT arm of the trial only) (see section 4.3 of this report). Overall survival, FACT-P, and adverse events are not included in the model.

Radiological PFS (rPFS) was the primary outcome of the ARANOTE trial, defined as time from randomisation to radiological progressive disease in soft tissue (RECIST v1.1 criteria) or bone (PCWG3 criteria), or all-cause death (CS Table 7). It was assessed every 12 weeks by BICR (CS Table 7), and results were reported for the primary completion analysis which had a median follow up of approximately 25 months which, our clinical expert confirms, is adequate time to assess response (CS section B.3.6.2).

rPFS is used as a surrogate outcome for OS in a sensitivity analysis of the company's ITC (CS section B.3.9.4.1 and section 4.3.6.2 of this report).

Overall survival (OS) was a key secondary outcome, defined as time from randomisation to all-cause death (CS Table 7). It was the first secondary outcome in the hierarchy for testing of statistical significance (CS Table 10) and as the OS results were not statistically significant (section 4.2.5.2 below) no further outcomes were tested for statistical significance in the ARANOTE trial. At the final analysis the median OS was [redacted] in either treatment arm (CS section B.3.6.3.1).

The results for the final overall survival analysis may be subject to confounding due to crossover of [redacted] participants from the placebo + ADT arm to the darolutamide + ADT arm. The EAG believe that it is appropriate to carry out adjustment for crossover because the crossover in the trial does not reflect the treatment pathway in clinical practice, although the company view the impact of crossover as minimal because there were only [redacted] deaths among the darolutamide crossover participants in the brief [redacted] crossover period (clarification response A5).

Published statistical methods, pre-specified in the trial's statistical analysis plan, were used to adjust for patient crossover in the ARANOTE trial following unblinding at the primary completion analysis. Two approaches were considered, the rank preserving structural failure time (RPSFT) and iterative parameter estimate (IPE) methods. These methods estimate the treatment effect as if patients in the placebo arm had never crossed over to darolutamide.

The company justify their selection of these methods in clarification response A6. They note that the RPSFT and IPE methods are two well-known methods used to adjust for crossover in randomised trials and are commonly used in NICE appraisals. They acknowledge that other methods can be used but note that "all such methods are subject to limitations". They do not elaborate on such limitations, including any applicable to their chosen methods (i.e. RPSFT and IPE). A discussion of the merits and limitations of the available adjustment methods in relation to the ARANOTE trial, including consideration of clinical plausibility would have given a stronger rationale for the company's selected adjustment methods.

The EAG invited the company to provide cross-over adjusted OS results using other available methods (e.g. featured in NCE DSU TSD number 16) if available (clarification question A7). The company responded that only the RPSFT and IPE methods were performed as there were very few OS events during the crossover period (between primary completion and final OS analysis). The company point out that the similar OS estimates the from RPSFT and IPE methods "provides confidence that the appropriate methodologies have been applied for these analyses." (clarification question A6). Whilst consistency in results is reassuring, it is only one consideration in choosing an appropriate analysis method. The EAG would have preferred to see of crossover adjusted OS estimates from all available methods to assess the degree to which they are consistent, as this would provide a more informed consideration of which adjustment methods, if any, are appropriate to inform decision making.

Time to deterioration in the Functional Assessment of Cancer Therapy – Prostate (FACT-P) total score is a pre-specified outcome (not primary or secondary) in ARANOTE which is used in the company's ITC. FACT-P is a validated patient reported outcome measure for patients with prostate cancer.[10] The ARANOTE trial defined deterioration as a decline of $\geq$10 points from baseline in the total score. This is a conservative use of the published estimate of clinically meaningful change that is six to 10 points in total score change;[11] and the time to deterioration is measured from randomisation (Clinical study report (CSR) section 5.1.4.3).

Adverse events are reported for the Safety Analysis Set (SAF) which consisted of all participants who received $\geq$1 dose of the study drug and participants were analysed according to the study drug they received (CS Table 9). Namely: darolutamide + ADT (double blind period), darolutamide + ADT (double-blind and open-label periods), placebo + ADT (double-blind period), placebo-darolutamide (crossover, i.e. open-label, period). Adverse events are reported according to the NCI-CTCAE v 5.0 criteria, and the results are

reported from the Final Analysis (CS section B.3.10). A pre-specified analysis of exposure adjusted incident rates (EAIRs) is also reported for ARTA-related adverse events, such as hypertension, flushing, diabetes, fatigue, and rash, during the double-blind study period (full list in CS Table 30; also considered as adverse events of special interest in CS Table 29).

EAG comment on outcomes assessment

The outcome measures included in the ARANOTE trial are similar to outcomes commonly used in oncology clinical trials, including rPFS and OS which were considered in the NICE technology appraisal of apalutamide + ADT in mHSPC (TA741). Caution is advised when interpreting the final OS estimates because the data are immature and subject to confounding due to crossover. Crossover adjusted OS estimates are available but do not necessarily represent estimates from alternative crossover adjustment methods.

4.2.5 Key efficacy results of the ARANOTE trial

All results (except for safety) are reported for the full analysis set (FAS), that is all randomised participants according to the treatment arm they were allocated at randomisation (CS Table 9) equivalent to an intention-to-treat (ITT) analysis. Safety results, including adverse events, are reported for the safety analysis set (SAF), see section 4.2.6.

4.2.5.1 Radiological Progression Free Survival (rPFS) – primary outcome

The results for rPFS are statistically significant and in favour of treatment with darolutamide + ADT (CS section B.3.6.2):

- At the primary completion analysis (after 222 events; data cut off 7 June 2024), participants treated with darolutamide + ADT had a 46% reduced risk of rPFS or death compared to participants in the placebo + ADT arm (HR, 0.54; 95% CI, 0.41 to 0.71; p<0.0001).
- At 24 months (within the double-blind period), the rPFS rate was 70% in the darolutamide + ADT arm compared to 52.1% in the placebo + ADT arm (median rPFS was not reached in the darolutamide + ADT arm).
-

Results for all the pre-specified subgroups were consistent with the results for the full analysis set (FAS). The subgroups for age ≥85, Black race, and presence of visceral metastases have wide confidence intervals due to small sample sizes (CS section B.3.7; CS Figure 10). The results for subgroups that could indicate high-risk disease, e.g. Gleason

score ≥8, high volume disease, presence of visceral metastases, are supportive of the positive effect of darolutamide + ADT.

4.2.5.2 Overall survival (OS) – key secondary outcome

Overall survival results are summarised in Table 5 below.

Table 5 ARANOTE overall survival results (darolutamide + ADT vs placebo + ADT; FAS)

Analysis	Risk reduction	Hazard Ratio	95% CI	p-value
Primary completion analysis (ITT) (163 events; data cut-off 7 June 2024)	19% [a]	0.81	0.59 to 1.12	0.1007
Final analyses				
ITT ([redacted] events; data cut-off [redacted])	[redacted]	[redacted]	[redacted]	[redacted]
RPSFT sensitivity analysis (to adjust for crossover)	[redacted] [a]	[redacted]	[redacted]	[redacted]
IPE sensitivity analysis (to adjust for crossover)	[redacted] [a]	[redacted]	[redacted]	[redacted]

Source*:* CS section B.3.6.3.1
Abbreviations: CI, confidence interval; FAS, full analysis set; IPE, iterative parameter estimate; ITT, intention to treat; RPSFT, rank preserving structural failure time.
[a] calculated by EAG.

Results for OS were not statistically significant, but they show a positive trend in favour of treatment with darolutamide + ADT; median OS was [redacted] in either treatment arm; sensitivity analyses to adjust for crossover to the darolutamide + ADT arm were consistent with the results from the final analysis (CS section B.3.6.3.1). Results for all pre-specified subgroups are [redacted] of darolutamide + ADT treatment (hazard ratios range from [redacted]), however as the confidence intervals for all subgroups [redacted] in the forest plot reported in Figure 5-2 of the Final Overall Survival Results Summary[9] the subgroup results are highly uncertain.

4.2.5.3 Other outcomes

Results for other secondary outcomes are also favourable to treatment with darolutamide + ADT compared to placebo + ADT, and they are reported in CS sections B.3.6.3.2 to B.3.6.3.6.

Results for time to deterioration in FACT-P, an outcome used in the comparative effectiveness NMA, are not reported in the CS. At the primary completion analysis, participants treated with darolutamide + ADT had an approximately [redacted]% reduced risk of deterioration in FACT-P total score compared to participants treated with placebo + ADT (HR [redacted]; 95% CI [redacted]; p[redacted]) (CSR section 5.1.4.3).

4.2.6 Key safety results of the ARANOTE trial

Safety results are reported in CS section B.3.10, with topline results reported in the Final Overall Survival Results Summary.[9]

A summary of treatment-emergent adverse events (TEAEs) in ARANOTE is reported in CS Table 27. It shows the rates for TEAEs are very similar across the darolutamide and placebo treatment arms for participants experiencing any adverse events, serious adverse events, Grade 3 or 4 adverse events, or Grade 5 adverse events, and AEs leading to permanent discontinuation. Slightly fewer dose modifications were reported in the placebo arm. The lower rates in the placebo-to-darolutamide group are explained by the shorter time frame of the post-crossover period.

The most common any-Grade TEAEs experienced by 10% or more participants were anaemia, arthralgia, urinary tract infection and back pain: the proportion of participants experiencing these in the darolutamide arm was almost identical pre- and post-crossover, and the proportion of participants in the placebo arm (double-blind period only) was slightly lower and, for back pain, about the same (CS section B.3.10.1).

The most common Grade 3 and 4 TEAEs in 5% or more participants were hypertension, anaemia, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT) and bone pain (CS section B.3.10.1). These are all adverse events related to ARTA treatments, but numbers of events were similar between the darolutamide and placebo arms.

TEAEs of special interest are those related to ARTA treatments. CS Table 29 shows that proportions of participants experiencing these adverse events was low ([redacted]) and they are similar between darolutamide and placebo arms. For fatigue and asthenia (weakness) rates are lower in the darolutamide arm compared to the placebo arm. When the results are adjusted for exposure (double blind trial period only), the incidence risk ratios for experiencing adverse events are lower in the darolutamide arm compared to the placebo arm not only for fatigue, but also for hypertension, diabetes mellitus, decreased weight, heart failure, depressed-mood disorder, and cerebral ischemia (CS Table 30).

EAG comment on safety results

Safety results from ARANOTE show darolutamide + ADT has a similar safety profile to placebo + ADT. For fatigue and weakness darolutamide + ADT was shown to be better than placebo + ADT. Fatigue and weakness do not tend to require hospitalisation and therefore these improvements do not necessarily incur cost savings, however the EAG's clinical expert advised that improvement relating to fatigue and weakness are of immense value to the patient.

4.2.7 Pairwise meta-analysis of intervention studies

No pairwise meta-analysis was conducted as there is only one relevant included study with results, the ARANOTE trial. The EAG concurs with the CS that a pairwise meta-analysis is currently not possible.

4.3 Critique of the indirect treatment comparison (ITC)

4.3.1 Rationale for ITC

The company's rationale for conducting an indirect treatment comparison (ITC) is based on the lack of direct, head-to-head evidence comparing darolutamide + ADT with the company's chosen cost-comparison treatment, apalutamide + ADT. The EAG agrees that an ITC is necessary to address the decision problem.

4.3.2 Identification, selection and feasibility assessment of studies for ITC

The CS reports that an ITC comparing darolutamide versus apalutamide (both in combination with ADT) is possible because both treatments have been compared to placebo + ADT in clinical trials (CS section B.3.9). There were two relevant placebo-controlled trials available for inclusion in the ITC, the TITAN trial[8 12] (apalutamide + ADT versus placebo + ADT) and the aforementioned ARANOTE trial[7] (darolutamide + ADT versus placebo + ADT). TITAN was the pivotal phase III multi-centre RCT which supported the regulatory approval of apalutamide + ADT in mHSPC and which informed NICE's recommendation for apalutamide as an option for treating mHSPC (TA741)[13] in 2021.

Although not explicitly labelled as such, the CS reports a feasibility assessment of the TITAN and ARANOTE trials as evidence to inform the ITC, considering factors such as comparability of the trial designs, the availability of outcome measure data, compatibility of outcome definitions, and methodological quality and risk of bias. (CS section B.3.9 and CS Appendix D Tables 16-20; clarification response A10).

4.3.3 Clinical heterogeneity assessment

In terms of patient characteristics, the CS compared the trials on factors including age, ethnicity, ECOG performance status, Gleason score, de novo disease, high volume disease and visceral metastases (CS Table 14). The CS comments that the trials are similar in terms of overall baseline characteristics, with exceptions for White ethnicity (around 10-13~~%~~ percentage points higher in TITAN), ECOG status 0 (higher in TITAN) and visceral metastases (just under 10 percentage points higher in ARANOTE). The EAG notes further differences between the trials not commented on in the CS, specifically high-volume disease (just under 10 percentage points higher in ARANOTE), and de novo disease (around 7 percentage points higher in TITAN). Overall. the above differences between the trials suggests that more patients in the ARANOTE trial have characteristics associated with worse prognosis and a potentially inadequate response to treatment than is the case for the TITAN trial population. This may potentially confound the results of the ITC, in favour of apalutamide + ADT. However, the magnitude of the differences in patient characteristics between TITAN and ARANOTE is relatively small (i.e. up to 10 percentage points difference) and thus any bias arising is unlikely to be substantial.

Most of the patient characteristics assessed in CS Table 14 are known prognostic factors and/or treatment effect modifiers in prostate cancer, though the CS does not explicitly identify them as such. The EAG invited the company to expand the list of patient baseline characteristics considered in CS Table 14, specifically to include any additional prognostic factors and effect modifiers (clarification question A11). The company responded that the list covers all key aspects and there were no further characteristics to add. Expert clinical advice to the EAG is that additional patient characteristics which should be considered include bone metastases (>4), PSA levels, presence of liver or lung metastases and haemoglobin and neutrophil counts.

4.3.4 Risk of bias assessment for studies included in the ITC

The company's assessment of bias for the ARANOTE trial is reported in CS Section B.3.5 (CS Table 11). As we have commented earlier (see section 4.2.3) we agree with the company that the trial is low risk of bias for outcomes measured at the primary analysis (prior to unblinding and patient crossover) but outcomes measured after primary analysis, i.e. OS and adverse events will be at increased risk of bias from performance bias and the effects of crossover from placebo + ADT to darolutamide + ADT. This is addressed in the CS using statistical adjustment methods to adjust for crossover (i.e. RPSFT and IPE methods), as discussed earlier in section 4.2.4.

The CS provides a risk of bias assessment for the TITAN trial using the University of York CRD critical appraisal criteria for RCTs (CS Appendix D1.3, Table 20). The company's conclusion is that "low risk of bias was found". The EAG has independently critically appraised the TITAN study using the same criteria and agrees with the company's judgement of low risk of bias overall. We previously assessed TITAN as at low risk of bias in in the EAG report for NICE TA741.[14] At that time interim results were available based on the double-blind randomised phase of the trial. Subsequently, the trial was unblinded and patients were permitted to crossover from placebo + ADT to apalutamide + ADT. A total of 208 of the 527 (39.4%) patients in the placebo + ADT arm crossed over to apalutamide + ADT. The final results of the TITAN trial are therefore potentially subject to high risk of performance bias and confounding because of crossover.[12]. However, as we note in the next section, a crossover adjusted estimate of OS from the trial has been reported.

4.3.5 Data inputs to the ITC

Separate evidence networks were constructed to estimate the relative effectiveness of the treatments for the following outcomes: rPFS, OS, time to deterioration in FACT-P, Grade 3-5 adverse events and discontinuation due to adverse events.

4.3.5.1 ARANOTE data inputs

The OS and adverse events analyses use ARANOTE data from the final OS analysis data cut-off from [redacted]. The rPFS and FACT-P analyses use data from the ARANOTE primary completion analysis data cut-off June 7th 2024. The rPFS and FACT-P outcomes were not intended to be updated at the [redacted] data cut, hence they have a slightly shorter median follow-up than the OS and adverse events analyses (median follow-up around 25 months compared to around [redacted], respectively).

The OS data used to inform the ITC were based on the ARANOTE full analysis population (analogous to a true ITT analysis) and not the crossover adjusted OS data reported in the CS (see section 4.2.5.2 of this report). Hence, the OS estimates for the placebo + ADT arm will be potentially confounded by survival outcomes in placebo patients who switched to darolutamide + ADT following study unblinding at the primary analysis in the trial. We discuss the implications of this for the results of the ITC below.

4.3.5.2 TITAN data inputs

The company clarified the source of the data inputs from the TITAN trial in clarification response A13. For the rPFS and FACT-P analyses, data from the primary analysis of TITAN [8] were used in the ITC, and for OS, Grade 3-5 adverse events and discontinuation due to adverse events, follow-up data from the final analysis set were used. [12] Hence, rPFS and

FACT-P analyses are based on shorter median follow-up than the OS and adverse events analyses (median follow-up around 24 months compared to around 44 months, respectively). The EAG notes the difference in median follow-up between the primary and final analyses in TITAN is larger than that of the ARANOTE trial, 20 months versus around [redacted], respectively.

As we mentioned earlier (section 4.3.4), the final OS estimates from TITAN are subject to the effect of patient crossover from placebo + ADT to apalutamide + ADT when the study was unblinded following the interim analysis. The journal publication of final analysis results from the trial.[12] reported a pre-planned sensitivity analysis using the inverse probability of censoring weights (IPCW) method to adjust for crossover. Under the IPCW method patients who crossed over from placebo to apalutamide were censored at the time of crossover, while patients remaining in the placebo group were weighted to compensate for missing data. The bias introduced by this informative crossover was corrected by weighting each patient by the inverse of their predicted probability of not being censored at a given time. The probability of crossover was determined by each patient's baseline characteristics in a logistic regression model. OS was then analysed with the censored data set and observations weighted by the inverse of the predicted probability of censoring.[12].

The OS HR for apalutamide + ADT vs placebo + ADT decreased from 0.65 (95% CI 0.53 to 0.79) to 0.52 (95% CI 0.42 to 0.64) when the IPCW adjustment was applied. Accordingly, the reduction in the risk of death with apalutamide increased from 35% to 48%, respectively, when the crossover adjustment was used. The EAG notes that the IPCW method is the only method of crossover adjustment mentioned in the trial publication, with no explicit rationale given for its use compared to other available methods. It is therefore unclear how consistent the crossover adjusted OS HR 0.52 (95% CI 0.42 to 0.64) is to OS estimates based on other adjustment methods.

4.3.5.3 Patient crossover adjustments

Importantly, the EAG notes that the ITC does not use the crossover adjusted estimates from the ARANOTE trial or the TITAN trial. Instead, the unadjusted ITT HRs from both trials are used as input parameters in the NMA.

In both trials, OS will be potentially confounded by placebo patients who switched to the experimental treatment (i.e. darolutamide + ADT, or apalutamide + ADT) following study unblinding. In each trial, the relative survival effects of the experimental treatment versus placebo will be potentially underestimated as a consequence. The CS does not mention whether crossover-adjusted OS HRs were considered for inclusion in the ITC and does not comment on the implications of using unadjusted OS HRs on the results of the ITC. The EAG suggests that all other things being equal, the use of unadjusted OS HRs will not bias the indirect comparison of darolutamide + ADT vs apalutamide vs ADT since in both trials the direction of bias is expected to be the same (i.e. underestimating the effect of the experimental treatment). However, differences in the magnitude of the bias between the trials may have an impact on the ITC. Specifically, the proportion of placebo patients who crossed over in TITAN (n=208/527; 39.4%) was [redacted] than in ARANOTE [redacted] and median follow-up was [redacted] (44 months versus [redacted] respectively). The implication is that the effect of crossover is likely to be greater in TITAN than in ARANOTE, due to more placebo patients crossing over and a longer follow-up period.

Differences in the impact of crossover are evident by comparing crossover adjusted and unadjusted OS HRs from the two trials (

Table **6**). There is little difference between the crossover adjusted and unadjusted HRs in the ARANOTE trial. The CS attributes this to very few deaths during the short time period between completion and final OS analysis [redacted] The difference in adjusted and unadjusted OS in TITAN is more pronounced and shows a greater reduction in the risk of death with apalutamide + ADT when crossover is adjusted for (unadjusted OS HR 0.65 (0.53 to 0.79); IPCW adjusted OS HR 0.52 (0.42 to 0.64), albeit using a different adjustment method to the ARANOTE trial. Given the fact that only selected crossover adjusted methods have been presented instead of a broader range of methods, the EAG considers it prudent to use the unadjusted ITT estimates from both trials in the base case ITC. However, the relative effectiveness of apalutamide + ADT versus placebo + ADT is underestimated by using the unadjusted estimate from TITAN (i.e. HR 0.65 vs HR 0.52). In turn this likely underestimates the true difference between darolutamide + ADT and apalutamide + ADT when compared indirectly, making them appear more similar than they actually are. The EAG would have liked to have seen sensitivity analyses using the crossover-adjusted OS estimate from TITAN (the IPCW methods plus any other available adjustment methods) to ascertain whether any significant differences in favour of apalutamide + ADT are detected. If so, it would weaken the case for a cost comparison appraisal because darolutamide would be inferior to apalutamide, at least in terms of OS.

Table 6 Crossover adjusted and unadjusted final OS estimates from the ARANOTE and TITAN trials

Trial ID, Treatments compared	**Proportion placebo patients crossed over, n/N (%)**	**Median follow-up (months)**	**Crossover unadjusted ITT HRs (95% CI)[a]**	**Crossover adjusted HRs (95% CI)**		
				Cross over adjustment method		
				RPSFT	**IPE**	**IPCW**
ARANOTE Darolutamide + ADT vs placebo vs ADT	[redacted]	31.4	[redacted]	[redacted]	[redacted]	NR
TITAN Apalutamide +ADT vs	208/527 (39.4)	44.0	0.65 (0.53 to 0.79)	NR	NR	0.52 (0.42 to 0.64)

Trial ID, Treatments compared	Proportion placebo patients crossed over, n/N (%)	Median follow-up (months)	Crossover unadjusted ITT HRs (95% CI)[a]	Crossover adjusted HRs (95% CI)		
placebo vs ADT						

Source: Table created by the EAG based on information in the CS, clarification question responses and the TITAN final survival analysis publication.[12]
Abbreviations: ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; IPCW, inverse probability of censoring weights; IPE, iterative parameter estimate; ITT, intention to treat; NR, not reported; RPSFT, rank preserving structural failure time.
[a] used in the company's ITC

4.3.6 Statistical methods for the ITC

The CS describes the ITC as a network meta-analysis (NMA) using a Bayesian generalised linear model framework, citing NICE Decision Support Unit (DSU) technical support document 2[15] (CS section B.3.9.1). The EAG notes this is a standard approach commonly used to conduct NMAs informing NICE technology appraisals. The NMA uses the relative treatment effects between each of the treatment comparisons in the network and estimates the surface under the cumulative ranking (SUCRA) and mean ranks of each treatment (apalutamide + ADT, darolutamide + ADT and placebo + ADT).

4.3.6.1 Random effects versus fixed-effects modelling

The CS states that both random effects and fixed-effect models were considered, and that the fixed-effect approach was the *a priori* preferred approach. The justification for this was the assumption that the random effects models would not converge because of lack of data, given that only two studies were included. Later in the CS it is reported the random effects models did converge (CS section B.3.9.3.1). The CS notes the lack of heterogeneity between the trials in patients' baseline characteristics, trial design, and outcome definitions as another reason for favouring a fixed-effect approach. The EAG considers this a reasonable justification, notwithstanding the minor differences in patient prognostic factors between the trials, as we discussed earlier (section 4.3.3).

Random effects and fixed-effect model fitting statistics using the deviance information criterion (DIC) are reported for each outcome measure (CS Tables 15, 17, 19, 21 and 23), and in each case the CS reports there were limited differences in the DIC between the random and fixed-effect models indicating that both fit the data well (CS Appendix D.1.4). Given the company's *a priori* preference they report fixed-effect model results in their base

case for all outcomes (CS section B.3.9.3). For transparency they also provide the NMA results based on random effects (CS Appendix D.1.7) and comment that these results are "aligned in conclusion". The EAG considers the CS has adequately reported and justified the approach to fixed versus random effects modelling and has no particular concerns.

4.3.6.2 Surrogacy analysis

The CS notes that a limitation of the NMA is that the ARANOTE trial was not statistically powered to detect a difference in OS between darolutamide + ADT and ADT + placebo (CS section B.3.9.2). The company therefore conducted a surrogate sensitivity analysis to predict OS, informed by guidance on evaluating surrogate endpoints from NICE DSU TSD number 20.[16] CS Appendix J gives a detailed account of the rationale for this analysis, and methods used to validate the surrogate outcome (rPFS). The key aspects of the process include conducting a systematic review of trials of all treatments for mHSPC, to examine the relationship between rPFS and OS; conducing a correlation meta-analysis; and use of simulation modelling via Markov Chain Monte Carlo simulation.

The EAG considers that the company have provided good transparency in reporting their implementation of the method. The analysis confirmed that rPFS meets NICE's criterion for surrogate validity. The results of the surrogacy analysis as applied to the ARANOTE trial are presented in the CS as a sensitivity analysis (CS section B.3.9.4.1), and are summarised in this report in section 4.4.3,

4.4 Results from the ITC

Below is a brief summary and EAG interpretation of the results of the ITC reported in the CS, for each outcome measure in turn. A summary tabulation of the ITC results can be found in Appendix 3.

4.4.1 rPFS

The fixed-effect indirect comparison of darolutamide + ADT and apalutamide + ADT resulted in a HR of [redacted] In this analysis an HR of [redacted] favours apalutamide + ADT, and the credible interval [redacted] confirming no statistically significant difference between the two treatments.

Apalutamide + ADT had the best mean rank of being effective (1.247 (95% CrI 0.998, 2.000)), with darolutamide + ADT having the second-best mean rank [redacted] and placebo + ADT ranked third [redacted]. The mean rank credible intervals for darolutamide + ADT and apalutamide + ADT overlapped.

The SUCRA values were 88%, [redacted] and [redacted] for the three treatments, respectively. The intervention with the highest SUCRA value would be regarded as the best, and in this case apalutamide + ADT is the best performing treatment of the three. The results of the random effects model were similar to the fixed-effect model, with wider credible intervals as would be expected.

4.4.2 OS

The fixed-effect indirect comparison of darolutamide + ADT and apalutamide + ADT resulted in a HR of [redacted] In this analysis an HR of [redacted] favours apalutamide + ADT, and the credible interval [redacted] confirming no statistically significant difference between the two treatments. Apalutamide + ADT had the best mean rank of being effective (1.169 (95% CrI 0.998, 2.000)) with darolutamide + ADT having the second-best mean rank ([redacted] with placebo + ADT ranked third [redacted]. The mean rank credible intervals for darolutamide + ADT and apalutamide + ADT overlapped. The SUCRA values were 92%, [redacted] and [redacted] for the three treatments, respectively indicating that apalutamide + ADT is the best performing treatment of the three. The results of the random effects model were similar, with wider credible intervals as would be expected.

4.4.3 Surrogate OS sensitivity analysis

As mentioned earlier (section 4.3.2) the company did a sensitivity analysis using surrogate OS estimates from ARANOTE and reported OS estimates for TITAN (CS Section B.3.9.4.1). The fixed-effect indirect comparison of darolutamide + ADT and apalutamide + ADT resulted in a HR of [redacted] In this analysis an HR of [redacted] favours apalutamide + ADT, but the credible interval [redacted] confirming no statistically significant difference between the two treatments.

The SUCRA and mean rank are [redacted] for apalutamide + ADT and darolutamide + ADT, with almost overlapping 95% CrIs on the latter (SUCRA 74% versus [redacted], respectively; mean rank 1.516 (1.000, 2.000) versus [redacted]

The surrogate OS sensitivity analysis was repeated using a random effects model (CS Appendix D, Section D1.7.6). Results were similar to the fixed-effect model, but with wider credible intervals, as predicted.

4.4.4 Time to deterioration in FACT-P

The fixed-effect indirect comparison of darolutamide + ADT and apalutamide + ADT resulted in a HR of [redacted], meaning that people treated with darolutamide + ADT are [redacted] more likely to experience a longer time to deterioration in FACT-P total score than people

treated with apalutamide + ADT. In this analysis an HR of [redacted] favours darolutamide + ADT, and the credible interval [redacted] confirming a marginal statistically significant difference between darolutamide + ADT and apalutamide + ADT.

Darolutamide + ADT had the best mean rank of being effective ([redacted]) with placebo + ADT having the second-best mean rank ([redacted] and apalutamide + ADT ranked third (2.565 (95% CrI 1.997, 3.004). The mean rank credible intervals for darolutamide + ADT and apalutamide + ADT did not overlap. The SUCRA values were [redacted], [redacted] and 22% for the three treatments respectively, indicating that darolutamide + ADT is the best performing treatment of the three. The results of the random effects model were similar to the fixed-effect model, with wider credible intervals, as would be expected. The point estimate results of the random effects model were similar to the fixed-effect model, but the wider credible intervals meant that the credible interval for the HR [redacted]. Therefore, the difference between darolutamide + ADT and placebo + ADT was no longer statistically significant and there is greater uncertainty due to considerably wider credible intervals (darolutamide + ADT vs apalutamide + ADT random effects HR [redacted] ([redacted].

4.4.5 Grade 3-5 adverse events

The fixed-effect indirect comparison of darolutamide + ADT and apalutamide + ADT resulted in a risk ratio (RR) of [redacted], meaning that people treated with darolutamide + ADT had a [redacted] reduction in the risk of experiencing Grade 3-5 adverse events than those treated with apalutamide + ADT. In this analysis a RR of [redacted] favours darolutamide + ADT, but the credible interval [redacted] confirming no statistically significant difference between the two treatments.

Placebo + ADT had the best mean rank for reduced risk of adverse events ([redacted]) with darolutamide + ADT having the second-best mean rank ([redacted] and apalutamide + ADT ranked third (2.842 (95% CrI 1.998, 3.002). The mean rank credible intervals for darolutamide + ADT and apalutamide + ADT overlapped. The SUCRA values were [redacted], [redacted] and 8% for the three treatments, respectively indicating that placebo + ADT is the best performing treatment of the three. The results for placebo + ADT and darolutamide + ADT are remarkably [redacted]. The results of the random effects model were similar to the fixed-effect model, with wider credible intervals, as would be expected.

4.4.6 Discontinuation due to adverse events

The fixed-effect indirect comparison of darolutamide + ADT and apalutamide + ADT resulted in a RR of [redacted] meaning that people treated with darolutamide + ADT had a [redacted] reduction in the risk of discontinuing treatment due to adverse events than people treated with apalutamide + ADT. In this analysis a RR of [redacted] favours darolutamide + ADT, and the credible interval [redacted] confirming a statistically significant difference between the two treatments.

Darolutamide + ADT had the best mean rank for lower risk of discontinuation due to adverse events ([redacted]) with placebo + ADT having the second-best mean rank ([redacted] and apalutamide + ADT ranked third (2.998 (95% CrI 2.998, 3.002). The mean rank credible intervals for darolutamide + ADT and apalutamide + ADT did not overlap. The SUCRA values were [redacted], [redacted] and 0% for the three treatments, respectively indicating that darolutamide + ADT is the best performing treatment of the three. The point estimate results of the random effects model were similar to the fixed-effect model, but the wider credible intervals meant that the credible interval for the risk ratio [redacted]Therefore, the difference favouring darolutamide + ADT was no longer statistically significant and there is less certainty in effects when a random-effects model is used.

4.4.7 Summary of the results from the ITC

The results from the fixed-effect analysis for efficacy relating to disease progression (rPFS) and survival (OS) show differences in treatment effects in favour of apalutamide + ADT. However, the differences are not statistically significant and should not compromise a cost-comparison analysis.

In contrast, the results of the fixed-effect analysis for quality of life (time to deterioration in FACT-P total score) and adverse events (Grade 3-5 AEs and discontinuation to AEs) show a difference in treatment effect in favour of darolutamide + ADT. The differences in treatment effect are statistically significant for time to deterioration in FACT-P total score and for discontinuation due to AEs. The selection of outcomes that illustrate the known tolerability of darolutamide may bias results in favour of treatment with darolutamide + ADT but interpreting the results as evidence of similarity for a cost-comparison analysis they highlight a small difference between the treatment effects of the intervention and comparator.

Results from the random effects analysis are similar to the fixed-effect models, in terms of point estimates, but none are statistically significant due to wider credible intervals estimated according to random effects assumptions.

Overall, the ITC results suggest no differences between darolutamide + ADT compared to apalutamide + ADT except for a couple of instances when statistically significant differences favoured darolutamide and ADT. This is consistent with the requirement for health technologies to provide similar or greater health benefits to existing recommended treatments. However, a caveat to this that the EAG's observation (discussed earlier in section 4.3.5.3) that, due to differences in the magnitude of patient crossover between the ARANOTE and TITAN trials, the ITC is underestimating the relative effect of apalutamide + ADT. We return to this issue in the following section.

4.4.8 Summary of EAG critique of the ITC methods

The ITC has several strengths but some key limitations which indicate uncertainty in the results and conclusions.

4.4.8.1 Strengths of the ITC

- The ITC is based on a comprehensive SLR which did a systematic search for relevant studies to facilitate an evidence network. The EAG is not aware of any relevant studies which were not identified.
- The two studies included are both pivotal phase III multi-centre, double-blind RCTs – the ARANOTE trial comparing darolutamide + ADT versus placebo + ADT, and the TITAN trial comparing apalutamide + ADT versus placebo + ADT. Both are well-designed trials at low risk of bias during the double-blind phase (but see limitations below).
- A reasonably comprehensive ITC feasibility assessment was undertaken, which gave particular attention to clinical heterogeneity. The trials are generally similar in design, and measurement of outcomes, and patient characteristics (but see below).
- The company's ITC is an NMA using a Bayesian generalised linear model framework to estimate the relative efficacy and safety of darolutamide +ADT versus apalutamide + ADT, based on NICE DSU TSD 2. This is a standard approach to NMA used in NICE technology appraisals. The model appears to have been implemented appropriately.
- The methods used in the NMA are well reported. The process of random effects versus fixed-effect model fitting and selection is transparent and well justified, and results from both models are available for all outcomes and show consistency in conclusions.

4.4.8.2 Limitations of the ITC

4.4.8.2.1 Effects of patient crossover

The EAG considers one of the main limitations of the ITC is that in both trials final OS is based on follow-up data collected in the open-label trial phase during which placebo patients crossed over to the experimental treatment.

- In both trials patients were analysed using an ITT approach, resulting in confounding in the placebo group estimates from inclusion of crossed-over patients receiving darolutamide / apalutamide. This potentially underestimates the relative effects of darolutamide/apalutamide + ADT versus placebo + ADT in the respective trials.
- Selected crossover adjusted OS estimates from the trials are reported but have not been included in the NMA. There is no discussion in the CS of the implications of using ITT or crossover adjusted effect estimates as input parameters. The EAG considers it appropriate in this current appraisal to use the unadjusted estimates in the NMA as a base case, since the direction of bias in in both is expected to be the same (i.e. underestimating the effect of the experimental treatment).

However, the magnitude of the bias appears to be larger in the TITAN trial, in which a higher percentage of placebo group patients crossed over to apalutamide and median follow up was longer. The ITT and crossover adjusted OS estimates are similar in the ARANOTE trial (see

- Table 6) but in the TITAN trial the crossover adjusted OS HR was noticeably lower than the ITT HR, illustrating underestimation in in the relative effects of apalutamide + ADT versus placebo + ADT in the trial.
- Using the ITT based rather than crossover adjusted OS estimates in the ITC potentially underestimates the relative efficacy of apalutamide compared to darolutamide. The crossover adjusted HR would likely result in a larger reduction in death favouring apalutamide, potentially shifting the upper bound of the current OS HR credible interval to less than 1, indicating a statistically significant difference.
- However, the EAG urges caution in the interpretation of the crossover adjusted estimates, because only a limited selection of adjustment methods were reported (two for the ARANOTE trial, and only one for the TITAN trial). It is unclear how robust the OS estimates are when adjusted according to methods using alternative assumptions.
- If crossover-adjusted OS estimates were used in the ITC this would be best viewed as an exploratory sensitivity analysis. The EAG considers the ITT based OS

estimates are more appropriate for the base case, bearing in mind the uncertainty outlined above regarding the potential underestimation of the relative effects of apalutamide + ADT in TITAN.

-

The results of the ITC for the rPFS outcome are not affected by crossover since they reflect only the double-blind phase of the trials. The relative effects of darolutamide + ADT versus apalutamide + ADT on rPFS can therefore be regarded as more certain.

4.4.8.2.2 Inferring similarity of effects

The CS states that the results of the ITC for rPFS show “no evidence of a difference” (CS page 70) between darolutamide + ADT and apalutamide + ADT, the implication therefore being that they demonstrate “similar efficacy” (CS page 5), hence supporting the company’s case for a cost comparison appraisal. The EAG agrees that most of the ITC analyses do not show a statistically significant difference between darolutamide and apalutamide, but this does not necessarily imply they are similar in effects. The most appropriate method of establishing similarity would be from an equivalence or non-inferiority trial directly comparing darolutamide + ADT versus apalutamide + ADT. Such a trial would require a large enough sample of patients to demonstrate equivalence or non-inferiority within pre-defined effect margins. The sample sizes of the respective ARANOTE and TITAN trials were set for the purpose of confirming superiority over placebo and are not necessarily sufficient for detecting equivalence / non-inferiority. In the absence of such a trial the ITC is nonetheless informative though its limitations should be taken into account.

5 COST COMPARISON MODEL

5.1 Model structure and assumptions

The company conducted a simple cost comparison analysis in Microsoft Excel comparing the drug acquisition costs of darolutamide + ADT with those of apalutamide + ADT in the treatment of adults with mHSPC. Patient outcomes over time were not modelled through a health economic model (such as adopting a Markov approach or a partitional survival modelling approach). The company further justified their simplified approach in their response to EAG clarification question B1, maintaining that the only difference between the intervention and comparator arms is the drug acquisition costs of darolutamide and apalutamide.

In their cost comparison analysis, the company made the following assumptions:

- No differences in the resource use to administer darolutamide and apalutamide
- No differences in treatment monitoring and managing adverse events between darolutamide and apalutamide

EAG comment on the model structure and assumptions

We view that it would be appropriate to provide a cost-comparison model that incorporated: i) clinical efficacy (e.g. survival estimates including PFS and OS); ii) costs (including, drug acquisition, drug administration, resource use, subsequent treatments, adverse events); iii) safety outcomes (e.g. adverse events); and iv) mortality. If the model included the above parameters it would enable the EAG to perform a robust verification of the model assumptions. Currently, the EAG are unable to test the impact of varying the parameter inputs such as resource use, subsequent treatments, and adverse events, on the overall cost-comparison results. However, based on the clinical evidence (discussed in section 4) and our expert's clinician's opinion, we view that darolutamide and apalutamide are likely to have similar effectiveness and resource use, as we will discuss in section 5.2.

5.1.1 Model features

The cost comparison analysis included the following features:

- **Population:** Adult men with mHSPC who are unsuitable for chemotherapy. This is narrower than the defined population in the NICE scope; the company restricts the patient population to those who cannot have docetaxel. The mean age of the modelled cohort is 69 years, based on the ARANOTE[17] trial.

- **Intervention:** Darolutamide with ADT. This aligns with the NICE scope.
- **Comparator:** Apalutamide with ADT. The EAG considers this to be acceptable. NICE TA741 recommends apalutamide for people with mHSPC who are unsuitable for chemotherapy. The company appear not to have considered enzalutamide with ADT as a comparator. They did not provide an explicit statement about why it was not considered, rather, they justified their chosen comparator, apalutamide, on the basis that it is recommended at the same point in the treatment pathway as is anticipated for darolutamide. The clinical experts advising the EAG viewed that enzalutamide and apalutamide are both commonly used in clinical practice.
- **Perspective**: The company state that the perspective for costing is that of the UK NHS and PSS. An NHS and PSS perspective is appropriate for the NICE Reference Case.
- **Time horizon**: effectively lifetime - 25 years (maximum age 100 years)
- **Cycle length**: 28-day cycle length
- **Half cycle correction:** Not applied
- **Discounting**: 3.5% per annum applied to drug acquisition.
- **Mortality**: The company assumes equal mortality across treatment arms. However, mortality is excluded from the analysis. This may be a reasonable assumption given that OS is similar between the two treatment arms (see section **Error! Reference source not found.**).

5.2 Model parameters

5.2.1 Time on treatment

The company uses time on treatment (ToT) in estimating the drug acquisition costs. Within the economic model, the proportion of patients on treatment in each cycle are multiplied by the drug acquisition costs. The CS states that the proportion of patients in the intervention arm were informed by the ARANOTE[17] trial and the same ToT was applied to the comparator.. Kaplan Meier curves for ToT for darolutamide + ADT along with the standard parametric models including exponential, Weibull, log-normal, log-logistic, Gompertz, Gamma and generalised gamma are presented in CS Figure 12; the corresponding Akaike Information Criterion (AIC) values in CS Table 31. The company applied the log-logistic curve in their base case and explored the use of gamma and generalised gamma in the scenario analyses. Furthermore, they conducted a scenario analysis where drug costs were adjusted based on radiographic PFS (rPFS), instead of ToT, assuming all patients would be treated up to progression or death, whichever occurred first. For this scenario, they applied

the log-normal distribution to extrapolate the rPFS Kaplan Meier curve for darolutamide + ADT, obtained from the ARANOTE trial.

EAG comment

Overall, we view the company's approach is reasonable. Estimating drug acquisition costs based on ToT is a conservative assumption, compared to that based on rPFS.

5.2.2 Drug acquisition costs

As stated in the previous section, ToT data from the ARANOTE trial was applied to the darolutamide and apalutamide arms to estimate the drug acquisition costs. The company justified their approach citing that there was an absence of ToT data for apalutamide. Information on dosing regimens, dose intensity and unit costs for the treatment arms are in CS Table 33. They used the list prices of the drugs from the British National Formulary (BNF)[18 19] and applied a confidential price discount of [redacted] on the price of darolutamide.

For ADT, the company applied the list prices obtained from the BNF. In response to clarification question B4, the company provided the information on dosing regimens, dose intensity and unit costs for the ADTs in Table 5 of the clarification response document. However, the EAG noted an inconsistency in the proportions of the constituent ADT treatments as reported in the CS and the economic model (shown in below in Table 7). In their response to clarification question B3, the company acknowledged the inconsistency and clarified that the values reported in the CS (which are based on NICE TA903[20] 'Darolutamide in combination with docetaxel and ADT') are appropriate. They corrected the values in their revised model submitted as part of the clarification response. This correction reduced the per capita cycle costs of ADT acquisition costs from £119.30 to £68.09 and administration costs from £435.98 to £238.96, respectively. However, the change does not impact the overall results of the cost comparison analysis as patients in both the treatment arms are assumed to have the same duration of treatment with ADT.

Table 7 Distribution of ADT treatments included in the model

Treatment	Administration route	Mix Proportion	
		CS	Economic Model
Degarelix	SC injection	Not reported	12.6%
Leuprorelin	SC injection	30.0%	54.0%
Goserelin	SC injection	30.0%	31.9%
Triptorelin	Oral	40.0%	1.5%
Buserelin	Oral	Not reported	0%

Source: CS model and CS B.4.2.3
ADT, Androgen deprivation therapy; SC, subcutaneous

The company assumed 100% relative dose intensity for darolutamide + ADT and apalutamide + ADT.

5.2.3 Drug administration costs

Drug administration costs were excluded in the model analysis as the company assumed the same rate of disease progression and ToT between darolutamide and apalutamide. Both darolutamide and apalutamide have oral administration with a daily dosing schedule. The ADT constituent treatments are the same for both the treatment arms.

5.2.4 Healthcare resource use and associated costs

Healthcare resource use (HCRU) is excluded from the cost-comparison analysis. The company state that darolutamide offers several benefits over apalutamide, leading to less resource use (such as, consultation with GPs, oncologists, pharmacists) and easier monitoring and patient management. The company argues that patients receiving apalutamide would require thyroid function tests as part of treatment monitoring as well as additional steps to ensure patient safety due to apalutamide's higher number of drug-drug-interactions. However, the company state that they have adopted a conservative approach and assumed comparable HCRU between the two treatments arms.

5.2.5 Adverse reaction unit costs and resource use

The economic model excluded any adverse event related costs and resource use. The CS presented the differences in adverse events associated with darolutamide + ADT in the ARANOTE trial compared to those of apalutamide + ADT in the TITAN trial in CS Table 34. Based on the ITC findings, the summary of the findings from the ARANOTE and TITAN trials, and their expert clinical opinions, the company argue that the safety profile of darolutamide is likely to be similar to, or better than, that of apalutamide.

EAG comment on model parameters

The model parameters are programmed correctly in the Excel spreadsheet. Expert clinical advice to the EAG supports the assumption that darolutamide is likely to require less health care resource and incur in fewer costs compared to apalutamide. However, we could not assess the impact of varying assumptions about resource use because this functionality is not included in the company model.

5.3 EAG model checks

The company did not mention model validation in their submission. The EAG checks of the company's cost comparison model included:

comparing all parameter values against the CS and the cited source documents;

checking the calculations in the MS Excel spreadsheet, and

double programming parts of the model, i.e., constructing a duplicate model version to check that it produced the same results.

We noticed that:

- the half-cycle modelling was not implemented.
- the administration costs were declared ("Treatment costs" sheet, cells M34 to R42), but not considered in the cost-comparison model. However, there is no effect in the model results as the intervention and comparator were assumed to have the same ADT regimen and ToT / rPFS curves.

We were able to reproduce the original model results (base case and scenarios). We confirm that the evidence sources and the values applied in the cost-comparison model are consistent with their sources, except for:

- A minor difference in the mean age (69 years old in the CS, 69.67 years old in the economic model, and 69.6 years old in ARANOTE CSR[17]). In response to clarification question C2, the company confirmed that the mean age is 69 years old and amended the model.
- There is a difference in the proportions of the constituent ADT treatments between the CS and the cost comparison model (see Table 7). In response to clarification question B3, the company stated that the correct proportions are presented in the CS and amended them in the model. The updated acquisition cost for the ADTs per cycle is £68.09, and the updated administration cost for the ADTs is £238.96.
- The company's base case results remained the same, as the discrepancies above did not affect the total incremental cost.

EAG comment on model checking and validation:

The cost-comparison model is generally well implemented. However, we spotted minor discrepancies between the CS and the original cost comparison model which the company duly corrected. The EAG has implemented the half-cycle correction in the corrected cost comparison model and presented the results in section 6.3 below.

6 COMPANY AND EAG COST COMPARISON RESULTS

6.1 Company cost comparison results

The total cost is based on the drug acquisition costs of the intervention, comparator and ADT medications and is shown in CS section B 4.3. The company base case results with the PAS discount price for darolutamide ([redacted]) and the list price for apalutamide and ADTs are in CS Table 35. The company's base case results with the list price for the intervention, comparator, and ADTs are in CS Table 36.

The results in CS Table 35 suggest that darolutamide + ADT [redacted] relative to apalutamide + ADT with the incremental cost of [redacted]. The company's corrections mentioned in section 5.3 did not affect the company's base case incremental costs but affected the ADT acquisition cost. Table 8 below shows the company base case updated results using the revised cost comparison model provided by the company with the clarification responses. The EAG notes that these analyses include the PAS price only for darolutamide, and list prices for apalutamide and the ADTs. We report results using the PAS discount prices for all treatments (where applicable) in a separate confidential addendum to this report.

Table 8 Company's base case updated results: PAS price for darolutamide and list price for apalutamide and ADT medications

	Darolutamide + ADT	Apalutamide + ADT	Difference
Drug acquisition	[redacted]	£146,218	[redacted]
Total cost	[redacted]	£146,218	[redacted]

Source: Revised cost comparison model
ADT, Androgen deprivation therapy; PAS, Patient access scheme

6.2 Company sensitivity and scenario analyses

The company did not provide deterministic and probabilistic sensitivity analyses. The EAG agrees that the cost comparison model parameters described in section 5.1 are more suited to scenario analysis as a method to explore uncertainty. The company scenario analyses are described in section CS section B.4.4. The scenario analyses results for darolutamide + ADT vs. apalutamide + ADT are in CS Table 37 (PAS price for darolutamide and list prices for apalutamide and ADTs) and CS Table 38 (list prices for darolutamide, apalutamide, and ADTs).

Considering the PAS price for darolutamide (CS Table 37), all scenarios [redacted] with the incremental cost varying from [redacted] The incremental cost remained the same when we ran the scenarios using the revised cost comparison model. Results with confidential price discounts for apalutamide and ADTs are reported in a confidential addendum to this report.

6.3 EAG's cost comparison results

Table 9 below shows the results with the EAG's correction to the company's cost comparison model, including the half-cycle correction mentioned in section 5.3. The incremental total cost varied from [redacted] to [redacted].

Table 9 EAG correction to the company base case updated results: PAS price for darolutamide and list price for apalutamide and ADT medications

	Darolutamide + ADT	Apalutamide + ADT	Difference
Drug acquisition	[redacted]	£145,022	[redacted]
Total cost	[redacted]	£145,022	[redacted]

Source: EAG corrected cost comparison model
PAS, Patient access scheme; ADT, Androgen deprivation therapy

6.4 EAG's scenarios

Table 10 below shows the company scenario results using the EAG corrected cost comparison model and EAG scenarios. For the EAG scenarios, we noticed that:

- The company's base case uses the log-logistic distribution (based on the lowest AIC model fit value) to model the ToT curve. Changing the ToT distribution curve varied the incremental total cost from [redacted].
- The company's scenario analysis, in which the drug cost adjustment was based on rPFS, has an incremental cost of [redacted] (scenario 6: log-normal, lowest AIC). Changing the distribution curve assigned to rPFS varied the incremental total cost from [redacted].
- Changing the discount rate from 3.5% to 1.5% resulted in an incremental cost of [redacted] (scenario 7).

The following scenarios did not affect the incremental cost result in the company's base case: varying mean age, varying the proportion of the ADTs, and the inclusion of the administration cost of the ADTs.

Table 10 Company and EAG scenarios: PAS price for darolutamide and list price for apalutamide and ADT medications

Base case	ID	Scenario	Darolutamide + ADT	Apalutamide + ADT	Incremental cost
EAG corrected base case result			[redacted]	£145,022	[redacted]
Company scenarios					
Time horizon: 25 years	1	10 years	[redacted]	£123,728	[redacted]
	2	15 years	[redacted]	£135,182	[redacted]
Discounting: 3.5%	3	No discounting	[redacted]	£173,565	[redacted]
Alternative ToT extrapolations: log-logistic	4	Gamma	[redacted]	£111,579	[redacted]
	5	Generalised gamma	[redacted]	£124,805	[redacted]
Drug cost adjustments based on ToT	6	Based on rPFS: log-normal	[redacted]	£204,363	[redacted]
EAG scenario					
Discount rate: 3.5%	7	1.5%	[redacted]	£159,810	[redacted]
Apply ToT adjustment: log-logistic extrapolation curve:	8	Exponential	[redacted]	£125,833	[redacted]
	9	Weibull	[redacted]	£144,128	[redacted]
	10	Log-normal	[redacted]	£160,133	[redacted]
	11	Gompertz	[redacted]	£104,064	[redacted]
Apply ToT adjustment: log-logistic	12	Apply rPFS: Exponential	[redacted]	£174,754	[redacted]
	13	Apply rPFS: Weibull	[redacted]	£199,916	[redacted]
	14	Apply rPFS: Log-logistic	[redacted]	£187,425	[redacted]
	15	Apply rPFS: Gompertz	[redacted]	£127,441	[redacted]
	16	Apply rPFS: Gamma	[redacted]	£144,465	[redacted]
	17	Apply rPFS: Generalised gamma	[redacted]	£249,018	[redacted]

Source: EAG corrected cost comparison model
ADT, Androgen deprivation therapy; EAG, External Assessment Group; PAS, Patient Access Scheme; rPFS, radiographic progression free survival; ToT, Time on Treatment

6.5 EAG's conclusion on the cost comparison

The company provided a cost comparison model that estimated only the difference in the drug acquisition costs between the darolutamide + ADT and apalutamide + ADT. Although this cost comparison model is aligned with the guideline ("User guide for the cost comparison company evidence submission template (PMG32)")[21], the EAG are unable to test the impact of varying the parameter inputs such as resource use, subsequent treatments, and adverse events, on the overall cost-comparison results.

The company's results suggest that, compared with apalutamide + ADT, darolutamide + ADT is associated with lifetime cost savings for patients with mHSPC when using the discounted PAS price for darolutamide and list price for apalutamide and ADTs (leuprorelin, goserelin and triptorelin). The EAG corrected the company's cost comparison model (see section 5.3), with marginal impact on the total cost (incremental total cost varied from [redacted] to [redacted]).

We report results for the company's and EAG's analysis using all available NHS price discounts for apalutamide and ADTs in a confidential addendum to this report.

7 EQUALITIES AND INNOVATION

The CS notes the presence of a small but significant equality gap in the mHSPC treatment pathway affecting people with a history of experiencing seizures or other predisposing factors. The currently available ARTAs are contraindicated in this group of people reducing their available treatment options to ADT monotherapy, which is considered sub-optimal by today's standards. The CS highlights that darolutamide has the potential to address this inequality as it is not contraindicated in such patients. As mentioned earlier, the EAG's clinical expert recognised that darolutamide can be used in people with seizures and other central nervous system disorders, although she also noted that such patients are rarely seen in clinical practice.

The disproportional impact of prostate cancer on particular population groups, notably Black males, older/elderly people and people with comorbidities is discussed in the CS. It is noted that treatment intensification (which refers to strategies to combine existing treatments with additional therapies, such as chemotherapy, to improve outcomes) decreases in these groups, though it is not explicitly stated why (e.g. contraindications/intolerance to adverse events/poor access to health care). The company point to the need for additional treatments for these groups, with darolutamide presumably filling this gap.

The CS does not explicitly discuss innovation in relation to darolutamide. By its nature, the cost comparison approach implies that the health technology under appraisal is not the first treatment of its kind. Rather, it shares similarities with current established therapies. The EAG suggests that, although darolutamide is not the first second-generation ARTA for treatment of mHSPC, its distinct chemical structure differentiates it from apalutamide and enzalutamide. Consequently, darolutamide is associated with reduced blood-brain barrier penetration and low central nervous system side effects, making it suitable for use in patients contraindicated to current treatments. This can be regarded as an innovative feature of darolutamide which adds value over current treatment options.

8 EAG COMMENTARY ON THE ROBUSTNESS OF EVIDENCE SUBMITTED BY THE COMPANY

The EAG considers the evidence submitted by the company appropriately supports a cost comparison appraisal. However, it is important to acknowledge the uncertainties discussed earlier.

The assumption that darolutamide and apalutamide are similar in efficacy and safety rests upon the company's ITC (NMA). The ITC uses standard methods and assumptions and for the most part is transparently reported. However, the ITC is limited by the sparse available data available on the relative efficacy and safety of darolutamide compared to apalutamide. ARANOTE and TITAN are well-designed multi-centre double blind RCTs but due to their designs there is potential for confounding in the final survival estimates, and for this to be carried through into the ITC. The ITC results showed no statistically significant difference between darolutamide and apalutamide across the various analyses undertaken, except for a couple of outcomes (one of which is adverse events), indicating the superiority of darolutamide over apalutamide. We have raised the possibility of darolutamide being found inferior to apalutamide in terms of OS but this remains to be tested. In the meantime the uncertainty remains.

Despite the above concerns the EAG is inclined to adopt a pragmatic view and suggest that, in the absence of further evidence, the similarities in chemical composition and mechanism of action shared by darolutamide and the other ARTAs, endorsed by expert clinical opinion, provides a sufficient basis upon which to assume general similarity in efficacy and safety, and thus support for a cost comparison appraisal.

A further issue is that it's not possible for the EAG to test the impact on survival, and of varying the cost comparison model parameter inputs, such as resource use, subsequent treatments, and adverse events. This is because the structure of the company's model does not cater for these analyses. However, based on clinical effectiveness evidence and expert clinical advice the EAG understands that darolutamide + ADT is likely to have similar efficacy, similar use of resources and costs (see sections 5.1 and 5.2) to apalutamide + ADT. Nonetheless, the EAG would prefer to be able to independently test these assumptions.

9 REFERENCES

1. NHS England. Clinical Commissioning Policy Statement: Docetaxel in combination with androgen deprivation therapy for the treatment of hormone naïve metastatic prostate cancer (B15/PS/a). Updated: 20 January 2016 [Available from: https://www.england.nhs.uk/wp-content/uploads/2016/01/b15psa-docetaxel-policy-statement.pdf?UNLID=106952065020223157562 4 accessed 22 October 2024.

2. EMA. Summary of Product Characteristics: darolutamide (NUBEQA) 2024 [updated 20-Dec-2024. Available from: https://www.medicines.org.uk/emc/product/11324/smpc/print.

3. NICE. Enzalutamide for treating hormone-sensitive metastatic prostate cancer. Technology appraisal guidance TA712, 07 July 2021.

4. BNF. British National Formulary: darolutamide drug interactions 2025 [Available from: https://bnf.nice.org.uk/interactions/darolutamide/ accessed 11 April 2025.

5. BNF. British National Formulary: enzalutamide drug interactions 2025 [Available from: https://bnf.nice.org.uk/interactions/enzalutamide/ accessed 11 April 2025.

6. BNF. British National Formulary: apalutamide drug interactions 2025 [Available from: https://bnf.nice.org.uk/interactions/apalutamide/ accessed 11 April 2025.

7. Saad F, Vjaters E, Shore M, Olmos D, Xing N, Pereira de Santana Gomes AJ, et al. Darolutamide in combination with androgen-deprivation therapy in patients with metastatic hormone-sensitive prostate cancer from the phase III ARANOTE trial. ESMO September 16, 2024. *J Clin Oncol* 2024;42(36):4271-81. doi: https://doi.org/10.1200/JCO-24-01798

8. Chi KN, Agarwal N, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. *N Engl J Med* 2019;381(1):13-24. doi: 10.1056/NEJMoa1903307 [published Online First: 20190531]

9. Bayer AG. Final Overall Survival Results Summary for Study 21140 (ARANOTE): A randomized, double-blind, placebo-controlled Phase 3 study of darolutamide in addition to androgen deprivation therapy (ADT) versus placebo plus ADT in men with metastatic hormone-sensitive prostate cancer (mHSPC). Data cut-off: 16 Jan 2025., 2025.

10. Esper P, Mo F, Chodak G, Sinner M, Cella D, Pienta KJ. Measuring quality of life in men with prostate cancer using the Functional Assessment of Cancer Therapy-prostate instrument. *Urology* 1997;50(6):920-28. doi: https://doi.org/10.1016/S0090-4295(97)00459-7

11. Cella D, Nichol MB, Eton D, Nelson JB, Mulani P. Estimating Clinically Meaningful Changes for the Functional Assessment of Cancer Therapy—Prostate: Results from a Clinical Trial of Patients with Metastatic Hormone-Refractory Prostate Cancer. *Value Health* 2009;12(1):124-29. doi: https://doi.org/10.1111/j.1524-4733.2008.00409.x

12. Chi KN, Chowdhury S, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, et al. Apalutamide in patients with metastatic castration-sensitive prostate cancer: final survival analysis of the randomized, double-blind, phase III TITAN study. *J Clin Oncol* 2021;39(20):2294-303. doi: 10.1200/JCO.20.03488 [published Online First: 20210429]

13. NICE. NICE Technology Appraisal TA741: Apalutamide with androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer – Technology appraisal guidance. October 28, 2021. 2021

14. Cooper K, Tikhonova I, Woods L, Hazel L, Souto Ribeiro I, Picot J, et al. Apalutamide for treating prostate cancer - A Single Technology Appraisal: Southampton Health Technology Assessments Centre, University of Southampton, 2020.

15. Dias SWNSA. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. Report by the Decision Support Unit 2011 (last updated September 2016), 2011.

16. Bujkiewicz S, Achana F, Papanikos T, Riley RD, Abrams KR. NICE DSU Technical Support Document 20: multivariate meta-analysis of summary data for combining treatment effects on correlated outcomes and evaluating surrogate endpoints. 2019. *Available from: https://wwwsheffieldacuk/nice-dsu/tsds/full-list* 2019

17. Bayer. Clinical Study Report: Phase 3 study of darolutamide in addition to ADT versus placebo plus ADT in men with mHSPC (ARANOTE). 2024

18. BNF. Darolutamide. Medicinal forms [Available from: https://bnf.nice.org.uk/drugs/darolutamide/medicinal-forms/ accessed 27/01/2025 2025.

19. BNF. Apalutamide. Medicinal forms [Available from: https://bnf.nice.org.uk/drugs/apalutamide/medicinal-forms/ accessed 27/01/2025 2025.

20. NICE. Darolutamide with androgen deprivation therapy and docetaxel for treating hormone-sensitive metastatic prostate cancer. Technology appraisal guidance [TA903] 2023 [Available from: https://www.nice.org.uk/guidance/ta903.

21. NICE. User guide for the cost comparison company evidence submission template (PMG32), 2017:41.

22. McKay RR, E. RA, A. PM, R. GJ, S. SS, Natasha L, et al. Darolutamide plus androgen-deprivation therapy: propensity score matching of ARASEC and historic clinical trial patients. *Future Oncology* 2025;21(11):1365-75. doi: 10.1080/14796694.2025.2482360

10 APPENDICES

Appendix 1 EAG appraisal of the clinical SLR methods

Table 11 Summary of the EAG appraisal of the clinical SLR methods

Systematic review components and processes	EAG response	EAG comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	Criteria for inclusion are organised according to a PICOD framework (CS Appendix Table 14). The criteria include all treatments for mHSPC, not only those relevant to this submission (CS Appendix D.1.1.2).
Were appropriate sources of literature searched?	Yes	MEDLINE (including In-process records), Embase and Cochrane databases were searched, additionally EBM Reviews, relevant conferences, and bibliographies of relevant systematic reviews and meta-analyses published in the last 6 years (CS Appendix D.1.1.1).
What time period did the searches span and was this appropriate?	Yes	An original search and three update searches were carried out covering from database inception to 24 October 2024 (CS Appendix D.1.1.1). There were no gaps in coverage, and they are reasonably up to date.
Were appropriate search terms used and combined correctly?	Yes	The search terms were comprehensive and relevant; they were combined appropriately in the databases (CS Appendix Tables 1 to 13).
Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	Yes	Criteria for inclusion are in CS Appendix Table 14. They are for a global SLR therefore include all treatments used for mHSPC. The excluded studies list consistently excluded ARANOTE, the pivotal trial, due to study design which raised concerns as to whether all relevant studies were identified. The EAG performed targeted searches in MEDLINE and ClinicalTrials.gov and identified the company ARASEC trial[22] which compares darolutamide + ADT compared to a matched historical control arm of ADT alone (derived from the CHAARTED RCT) for treating men with mHSPC in the United States. The trial publication was published after the last search date, but we identified it via ClinicalTrials.gov (NCT05059236). This study could potentially contribute evidence to an ITC

Systematic review components and processes	EAG response	EAG comments
		however, the company confirmed that the completion date for the primary outcome is not expected until Q2 2025, with data available in Q4 2024 9clarification response A16). Therefore, we are now confident that all studies with results relevant to this appraisal were identified.
Were study selection criteria applied by two or more reviewers independently?	Yes	Studies were screened by two reviewers independently with any discrepancies resolved by a third reviewer (CS Appendix D.1.1.2).
Was data extraction performed by two or more reviewers independently?	Unclear	The procedure for conducting data extraction is not reported in either CS Appendix D or CS section B.3.
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Yes	The company assessed the ARANOTE trial using the NICE checklist for RCTs (CS section B.3.5).
Was risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	Unclear	The number of reviewers conducting the quality assessment is not reported in either CS Appendix D or CS section B.3.5.
Is sufficient detail on the individual studies presented?	Yes	The company provided the relevant clinical study reports for ARANOTE and all relevant published papers with the main submission and the study SAP and protocol for ARANOTE with the clarification response.
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Yes	An NMA carried out to compare effectiveness and safety of darolutamide + ADT with apalutamide + ADT. The NMA is discussed in section 4.3 of this report.

Abbreviations: ADT, androgen deprivation therapy; EBM, Evidence Based Medicine Reviews database; ITC, indirect treatment comparison; mHSPC, metastatic hormone-sensitive prostate cancer; NMA, network meta-analysis; PICOD, Population Intervention Comparator Outcomes Design-of-study framework; RTCs, randomised controlled trials; SAP, statistical analysis plan; SLR, systematic literature review.

Appendix 2 Risk of bias assessment for ARANOTE

Table 12 Company and EAG risk of bias assessment for the ARANOTE trial

NICE checklist criteria	Company assessment	EAG assessment
Was randomisation carried out appropriately?	Yes. Randomisation was appropriate and carried out centrally using an Interactive Web Response System (IWRS) system.	Yes, agree. Low risk of bias
Was the concealment of treatment allocation adequate?[a]	Yes. The study was double-blinded such that neither the investigator or study site personnel, the study sponsor or participant knew which drug was being administered. The appearance of darolutamide and placebo were identical, and study drugs were packed in bottles labelled with a unique kit number assigned to the participant via IWRS.	Yes, agree. We assume that the IWRS system ensured that the process of treatment allocation was adequately concealed. **Low risk of bias.**
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Patient characteristics were well balanced between the two groups.	Yes, agree. All participant characteristics were similar between groups, including prognostic factors for mHSPC such as disease volume, disease pattern (Gleason score) and presence of visceral metastases. **Low risk of bias.**
Were the care providers, participants and outcome assessors blind to treatment allocation? [b]	Yes, it is a double-blind study.	Yes, agree for outcomes reported at the primary data analysis. The primary analysis is based on assessments made during the double-blind trial period. For rPFS it is also based on BICR. **Low risk of bias for the primary outcome of rPFS.**

NICE checklist criteria	Company assessment	EAG assessment
		Unblinding occurred after the primary completion analysis when participants in the placebo arm were permitted to crossover to darolutamide in the open-label study period. **High risk of bias for outcomes assessed after the primary analysis (i.e. final analyses of OS and adverse events)**
Were there any unexpected imbalances in drop-outs between groups?	No. Authors reported the number of patients and reasons for discontinuation in both treatment groups and these were balanced between groups.	No, agree. However, at the primary completion analysis, more participants in the placebo arm (71.7%) discontinued the study drug than in the darolutamide arm (45.5%). (CS Appendix Figure 2). The biggest cause of discontinuations was disease progression, and was highest in the placebo group, as would be expected in a placebo controlled trial. The remaining reasons for discontinuation are reasonably balanced between arms. **Low risk of bias.**
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. Authors measured and reported all the outcome as per study primary and secondary endpoints stated in method section.	No, agree. CSR is comprehensive for all outcomes. **Low risk of bias.**
a) Did the analysis include an intention-to-treat analysis? b) If so, was this appropriate?	Yes. This was a FAS analysis for measuring efficacy and mITT for safety outcomes, but no methods were used to account for missing data.	a) Yes, agree. The FAS analysis for efficacy outcomes is analogous to a true ITT analysis. No, disagree for the safety outcomes. The CS refers to

NICE checklist criteria	Company assessment	EAG assessment
c) Were appropriate methods used to account for missing data? [c]		a Safety Analysis Set (SAF) for safety outcomes defined as all participants randomised who took ≥1 dose of study drug. Participants were analysed according to the study drug they received. This is not compatible with an ITT analysis. b) Yes, agree for efficacy outcomes. Yes, agree for safety outcomes. The company's definition of the SAF is similar to that used in other clinical trials and appropriate for attributing adverse events to study drugs. c) No methods were used to account for missing data, with appropriate exceptions reported in CS Table 10. The amount of missing data is not reported so it is unclear whether methods of handling missing data were necessary. **Unclear risk of bias.**

Source: CS Table 11 with added EAG comments; ARANOTE trial publication;[7] ARANOTE Final OS Summary.[9]

[a] The company's justification for answering 'yes' to this question appears to conflate study blinding with allocation concealment. These are two separate procedures in clinical trials, that can lead to different types of bias. See also footnote [b].

[b] The company's justification for their answer to whether allocation concealment was adequate, given earlier in the table (see footnote [a]) is more appropriate as an explanation for their answer to this question on study blinding.

[c] The EAG have split what was a single compound question into three sub-questions (i.e. a, b and c) to enable us to make judgements specific to each sub-question. In contrast, the company's judgements reflect their answer to the original single compound question.

Abbreviations: BICR, blinded independent central review; CSR, clinical study report; FAS, full analysis set; IWRS, Interactive Web Response System; mHSPC, metastatic hormone-sensitive prostate cancer; mITT, modified intention to treat; rPFS, radiographic progression free survival.

Appendix 3 Summary of ITC results

Table 13 Summary of ITC results

Treatment / Outcome	Fixed effects (company base case)				Random effects (company scenario analysis)			
	HR/RR [a] (95% CrI)	SUCRA	Mean rank (95% CrI)	EAG comment	HR/RR [a] (95% CrI)	SUCRA	Mean rank (95% CrI)	EAG comment
rPFS (Hazard Ratio <1 favours apalutamide)								
Apalutamide + ADT	Comparison	0.88	1.247 (0.998, 2.000)	Favours APA; NS	Comparison	0.82	1.370 (1.000, 2.000)	Favours APA; NS
Darolutamide + ADT	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
Placebo + ADT	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
Overall survival [b] (Hazard Ratio <1 favours apalutamide)								
Apalutamide + ADT	Comparison	0.92	1.169 (0.998, 2.000)	Favours APA; NS	Comparison	0.86	1.287 (0.999, 2.732)	Favours APA; NS
Darolutamide + ADT	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
Placebo + ADT	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
Time to deterioration in FACT-P (Hazard Ratio >1 favours comparator vs apalutamide)								
Darolutamide + ADT	[redacted]	[redacted]	[redacted]	Favours DAR; SS	[redacted]	[redacted]	[redacted]	Favours DAR; NS
Placebo + ADT	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
Apalutamide + ADT	Comparison	0.22	2.565 (1.997, 3.004)		Comparison	0.35	2.294 (1.000, 3.002)	
Grade 3-5 AEs (Rate Ratio <1 favours comparator vs apalutamide)								
Placebo + ADT	[redacted]	[redacted]	[redacted]	Favours DAR; NS	[redacted]	[redacted]	[redacted]	Favours DAR
Darolutamide + ADT	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	

Treatment / Outcome	Fixed effects (company base case)				Random effects (company scenario analysis)			
	HR/RR [a] (95% CrI)	SUCRA	Mean rank (95% CrI)	EAG comment	HR/RR [a] (95% CrI)	SUCRA	Mean rank (95% CrI)	EAG comment
Apalutamide + ADT	Comparison	0.08	2.842 (1.998, 3.002)		Comparison	0.33	2.338 (1.000, 3.002)	over APA; NS
Discontinuation due to AEs (Rate Ratio <1 favours comparator vs apalutamide)								
Darolutamide + ADT	[redacted]	[redacted]	[redacted]	Favours DAR; SS	[redacted]	[redacted]	[redacted]	Favours DAR; NS
Placebo + ADT	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
Apalutamide + ADT	Comparison	0.00	2.998 (2.998, 3.002)		Comparison	0.08	2.834 (1.000, 3.002)	

Source: reproduced from CS Tables 16, 18, 20, 22 and 24; CS Appendix D.1.7 Tables 28, 29, 30, 31 and 32.
Abbreviations: ADT, androgen deprivation therapy; AEs, adverse events; APA, apalutamide; CrI, credible interval; DAR, darolutamide; HR, hazard ratio; ITC, indirect treatment comparison; NS, not statistically significant; RR, rate ratio; SS, statistically significant; SUCRA, surface under the cumulative ranking curve.
[a] Hazard Ratio or Rate Ratio as indicated in the treatment/outcome column.
[b] ITT analysis inputs

Single Technology Appraisal

Darolutamide with androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer [ID6452]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Wednesday 18 June 2025** 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.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Description of cost comparison model methodology

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 4.2.4 (page 22) states that "The ARANOTE trial outcomes are not incorporated into the cost comparison model", however, the cost comparison model does include ToT and rPFS data from the darolutamide + ADT arm of the ARANOTE trial"	Please amend this sentence to: "The cost comparison model only includes time on treatment and rPFS from the darolutamide + ADT arm of the ARANOTE trial"	To correctly reflect the cost comparison model	We have updated the text which now says: "The ARANOTE trial outcomes incorporated into the cost comparison model are time on treatment and rPFS (from the darolutamide + ADT arm of the trial only) (see section **Error! Reference source not found.** of this report). Overall survival, FACT-P, and adverse events are not included in the model"

Section 5.2.1 (page 41) "The CS stated that these proportions of patients on both the treatment arms (intervention and comparator) were informed by the ARANOTE[17] trial." The Company would like to clarify that the assumption for ToT for the intervention was based on the ARANOTE trial, and this same ToT was applied to the comparator arm. However, the EAG's wording may give the impression that both treatment arms were directly informed by the ARANOTE trial, which is inaccurate, as only the intervention arm was represented in that trial.	Please amend this sentence to: "The CS stated that the proportions of patients receiving darolutamide + ADT was informed by the ARANOTE[17] trial and were equally applied to the apalutamide + ADT."	To correctly reflect the cost comparison model	Thank you for highlighting this. We have revised the text to clarify that the ToT for the intervention arm was based on the ARANOTE trial and the same ToT was applied to the comparator arm.

Section 5.2.1 (page 41) *"*Kaplan Meier curves for ToT for darolutamide + ADT along with the standard parametric models including exponential, Weibull, log-normal, log-logistic, Gompertz, and generalised gamma are presented in CS Figure 12; the corresponding Akaike Information Criterion (AIC) values in CS Table 31." The Gamma distribution was one of the parametric functions used in the cost-comparison analysis and was also tested in the scenario analysis. Therefore, should be included here.	Please amend this sentence to: *"*Kaplan Meier curves for ToT for darolutamide + ADT along with the standard parametric models including exponential, Weibull, log-normal, log-logistic, Gompertz, **Gamma** and generalised gamma are presented in CS Figure 12; the corresponding Akaike Information Criterion (AIC) values in CS Table 31"	To correctly reflect analyses completed	Thank you for highlighting this. We have now inserted the missing parametric function within the sentence.

Issue 2 Reference to wrong trial

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG comment**
Section 4.3.3 (page 28) states	Please amend to: ", and de novo disease (around 7 percentage points higher in TITAN)."	To correctly reflect the trial data	Thank you for highlighting this error; this is now corrected.

", and de novo disease (around 7 percentage points higher in ARANOTE)." However, CS Table 14 reports 71.1% and 75.3% of patients in the respective arms of the ARANOTE trial, and 78.3% and 83.7% in the TITAN trial have de novo disease, so this is higher in the TITAN trial			

Issue 3 Unclear description of issue

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 8 (page 50), final paragraph on the page states: "A further issue is that it's not possible for the EAG to test the impact on survival of varying the cost comparison model parameter inputs, such as resource use, subsequent treatments, and adverse events."	Amend to a clearer sentence, possibly: "A further issue is that it's not possible for the EAG to test the impact on survival**, and** of varying the cost comparison model parameter inputs, such as resource use, subsequent treatments, and adverse events."	To clarify the issue discussed by the EAG	Thank you for highlighting the typographical error. This has now been amended, as suggested by the company.

It is unclear to the company what the EAG meant to say here.			

Issue 4 Unclear description of cross-over data

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 4.2.4 **"**The EAG believe that it is appropriate to carry out adjustment for crossover because the crossover in the trial does not reflect the treatment pathway in clinical practice, although the company view the impact of crossover as minimal because there were only [redacted] deaths in the brief [redacted] crossover period (clarification response A5)" There were [redacted] deaths in the open label extension across the treatment arms, this presentation may lead the reader to misinterpret results	Please amend to: "of crossover as minimal because there were [redacted] only deaths in the darolutamide crossover patients."	To correctly reflect the trial data	Thank you for highlighting this, we agree to the requested amendment to avoid misinterpretation of the data. Correction made.

Issue 5 Unclear description of ARANOTE study

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment

Section 4.2.3, page 21 **“**Outcomes reported after the primary completion analysis, that is, final OS and final adverse events we regard as at high risk of bias” “however, OS and adverse event outcomes that were assessed after the primary completion analysis (clarification response A3) are at high risk of performance bias and unclear risk of attrition bias” Table 12, page 58 “High risk of bias for outcomes assessed after the primary analysis (i.e. final analyses of OS and adverse events)” We acknowledge that the risk of bias can increase within an open label extension of an RCT. We consider the use of **high risk of bias** may be open to misinterpretation by the reader, especially in relation to OS, an objective endpoint.	Please amend “high risk of bias” to “higher risk of bias”	To reduce misinterpretation of the trial data	Not a factual error. The EAG’s assessment of ‘high’ risk of performance bias summarises the risk of bias for both the OS and safety results at the final analysis. We acknowledge that OS is an objective endpoint, however in terms of performance bias, the nature of an open label study can influence aspects of patient care or lifestyle that may affect survival. Other types of bias are also applicable to OS, but we focused on performance bias in our assessment. The convention in assessing risk of bias is to judge bias as ‘high’, ‘low’ or ‘unclear’. These are established categories and

			introduction of a 'higher' category increases the likelihood of misinterpretation. No change made.

Minor typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
1. *Table 4, Row 4 Pre-specified subgroups* – Age is missing subgroup of 75-84 2. *Table 4, Row 13 Main analyses* – incorrect database cut off date presented "June 2024, database lock July 2024" 3. *Section 8, page 50*: "the structure of the company's model does cater for"	1. Update Age categories Age (<65/65-74/75-84/≥85) 2. Amend to "database lock June 2024" 3. Amend to "the structure of the company's model does **not** cater for"	These are only minor typographical errors and will not impact the results	1. Thank you. This is now correct. 2. Thank you. This is now correct. 3. Thank you. This is now correct.