

5.05 DAROLUTAMIDE, Tablet 300 mg, Nubeqa[®], Bayer Australia Ltd.

1 Purpose of submission

- 1.1 The submission requested a General Schedule Authority Required (Telephone) listing for darolutamide for treatment of patients with non-metastatic castration resistant prostate cancer (m0CRPC) at high risk of distant metastases. This was the first PBAC submission for darolutamide.
- 1.2 Listing was requested on the basis of a cost-utility analysis versus standard of care (SOC). The key components of the clinical issue addressed by the submission are presented in Table 1.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Patients with m0CRPC who are at high risk of developing distant metastases; with high risk defined as a PSADT ≤ 10 months
Intervention	Darolutamide 600 mg (2 × 300 mg) twice daily (total dose 1200 mg/day) with background ADT
Comparator	Main comparator: watchful waiting (SOC) with ongoing ADT Near-market comparators: apalutamide 240 mg/day; enzalutamide 160 mg/day
Outcomes	MFS, OS, time to pain progression, time to initiation of first cytotoxic chemotherapy, time to first symptomatic skeletal event, patient-reported outcomes, safety
Clinical claim	Superior efficacy and inferior safety vs. watchful waiting (SOC) Non-inferior efficacy and superior safety vs. apalutamide and vs. enzalutamide

Source: Table 1-1, p5 of the submission.

ADT=androgen deprivation therapy; m0CRPC=non-metastatic castration-resistant prostate cancer; MFS=metastasis-free survival; OS=overall survival; PSADT=prostate-specific antigen doubling time; SOC=standard of care

2 Background

Registration status

- 2.1 Darolutamide was TGA registered on 26 February 2020. It was evaluated by the TGA under a work-sharing initiative with Health Canada. The TGA Delegate's Overview was provided in the submission; however, a Clinical Evaluation Report was not produced under the work-sharing initiative. Darolutamide was not considered at an Advisory Committee on Medicines meeting.

Previous PBAC consideration

- 2.2 While there has been no previous consideration of darolutamide by the PBAC, there have been two considerations of apalutamide for the treatment of m0CRPC. Table 2

provides a summary of PBAC concerns around the clinical and economic evidence for apalutamide, including comments describing the approach adopted for darolutamide.

Table 2: Summary of PBAC concerns with apalutamide

Paragraph/date (apalutamide PSD)	Matter of concern
Paragraph 7.8 November 2018	PBAC considered that the claim of improvement in OS was not adequately supported by the clinical data. PBAC considered that the claim of improvement in MFS, rPFS and sPFS was reasonable but the magnitude of benefit was highly uncertain given the immaturity of the data.
Paragraph 7.3 July 2019	The resubmission proposed that the PBS restrictions should allow abiraterone to be used after apalutamide, and presented longer-term PFS2 data from the SPARTAN trial. Overall, the PBAC considered that the PFS2 data do not provide information as to whether the magnitude of the benefit of abiraterone versus placebo would remain unchanged with prior use of apalutamide. The PBAC advised that the PBS restrictions should not allow abiraterone to be used after apalutamide.
Paragraph 7.4 July 2019	The resubmission stated that it may be reasonable to preclude the use of PBS-subsidised enzalutamide after apalutamide, as there is potential for cross-resistance and it is unlikely that enzalutamide would demonstrate efficacy following progression on apalutamide given their pharmacological similarity. The PBAC agreed, and advised that that the PBS restrictions should not allow enzalutamide to be used after apalutamide. The darolutamide submission assumed that neither abiraterone nor enzalutamide will be permitted to be used following darolutamide treatment and this approach was reflected in the economic model and financial estimates.
Paragraph 7.7 July 2019	The PSCR presented updated OS data from 'interim analysis 2' of the SPARTAN trial.....however, the magnitude of the benefit remained uncertain as the data were immature (median OS was not yet reached in either arm).
Paragraph 7.1 July 2019	The PBAC considered that the incremental cost-effectiveness ratio (ICER) was high and uncertain, and that a price reduction would be required to bring the ICER into an acceptable range.
Paragraph 7.13 July 2019	The PBAC advised that the base case of the economic model should include the following revisions: use BICR-assessed MFS; use a 10-year time horizon; include updated TTD data if available; use unadjusted OS results (i.e. do not include any adjustments for treatment switching) given the uncertain magnitude of the OS gains. The darolutamide model applied these recommendations.

Source: November 2018 and July 2019 apalutamide PSDs.

MFS=metastasis-free survival; OS=overall survival; PFS2=progression-free survival for first subsequent therapy; rPFS=radiographic progression-free survival; PSCR=Pre-Subcommittee Response; PSD=public summary document; sPFS=symptomatic progression-free survival; TTD = time to treatment discontinuation

3 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	DPMQ	Proprietary Name and Manufacturer
DAROLUTAMIDE Tablet, 300 mg	112	5	Published: \$ [REDACTED] Effective: \$ [REDACTED]	NUBEQA®, Bayer
Category/ Program:	GENERAL – General Schedule (GE)			
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners			
Condition:	Castration resistant carcinoma of the prostate			
PBS indication:	Castration resistant carcinoma of the prostate			
Treatment phase:	Initial			
Restriction:	<input checked="" type="checkbox"/> Authority Required – Telephone/Online			

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Clinical criteria:	Patient must not have distant metastasis on conventional imaging AND Treatment must be used in combination with androgen deprivation therapy AND Patient must have a PSA doubling time of 10 months or less AND Patient must have a WHO performance score of 0 or 1 AND Patients who have progressive disease while on this drug are no longer eligible for PBS-subsidised treatment with this drug
Treatment phase:	Continuing
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Treatment must be used in combination with androgen deprivation therapy AND Patients who have progressive disease while on this drug are no longer eligible for PBS-subsidised treatment with this drug
Prescriber Instructions:	The PSA doubling time must have been calculated using at least three PSA values obtained during androgen deprivation therapy
Administrative Advice:	Special Pricing Arrangements apply No increase in the maximum quantity or number of units may be authorised No increase in the maximum number of repeats may be authorised

- 3.1 The requested restriction is similar to the restriction for apalutamide in the July 2019 Public Summary Document (PSD) and includes modifications suggested by the PBAC Secretariat. Previous PBAC advice from the July 2019 apalutamide submission stated that the abiraterone and enzalutamide PBS restrictions would be updated to exclude abiraterone or enzalutamide use after apalutamide (paragraphs 7.3 and 7.4, July 2019 apalutamide PSD) had apalutamide been recommended. The PBAC considered this action would be appropriate to uphold for darolutamide, noting that there is limited evidence to support use of abiraterone or enzalutamide following darolutamide (only 3.2% of all darolutamide-treated trial patients received enzalutamide or abiraterone as subsequent therapy).
- 3.2 Accounting for the price proposed in the submission and the efficacy results of the clinical trial evidence, the requested restriction limits use to patients who are at high risk of distant metastases, (i.e. patients with a prostate-specific antigen (PSA) doubling time of 10 months or less) in an attempt to target PBS subsidy to a patient population in which darolutamide would be considered cost-effective. The PBAC considered that at the proposed price and claimed clinical benefits, treatment should be further restricted to patients with a PSA level of at least 2 ng/mL, noting that PSA doubling time alone is not always an indicator of risk and a PSA level of at least 2 ng/mL was an inclusion criterion in the ARAMIS trial. In addition, the PBAC agreed with ESC and considered that restricting treatment to patients with a PSA level of at least 2 ng/mL would help limit darolutamide use to higher risk patients who are more likely to benefit from treatment.

- 3.3 The ESC considered that prostate-specific membrane antigen (PSMA) PET scanning, whilst not MBS subsidised, is an increasingly common staging modality for m0CRPC, and is standard of care in many centres in Australia. The ESC noted that PSMA screening is more sensitive compared to conventional imaging which could result in patients otherwise classified as m0CRPC being classified as having occult metastatic disease. As such, the ESC considered that a lower risk patient population, as compared to the ARAMIS trial population, who may not benefit from treatment could become eligible for darolutamide if it was PBS listed. The PBAC considered that the reference to conventional imaging was appropriate.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 In men with prostate cancer, biochemical progression, as signified by rising serum PSA despite androgen deprivation therapy (ADT), and in the absence of radiologically detectable metastases, defines the clinical state referred to as m0CRPC. Patients with m0CRPC who have a PSA doubling time ≤ 10 months are considered to be at high risk of developing metastases. These patients are currently managed with ADT with possible use of secondary hormonal therapies.
- 4.2 It is expected that approximately one-third of all patients with m0CRPC will develop metastases within two years, with more than half becoming metastatic within three years. Once metastases occur, the disease becomes incurable and median survival has been estimated to be 16 to 30 months. The submission noted that many patients will require the initiation of cytotoxic chemotherapy to delay the occurrence of further metastasis, which can result in highly undesirable adverse events that further add to the treatment burden.
- 4.3 The submission concluded that there is a need for effective therapies which can delay the onset of metastatic disease, avoid the need for cytotoxic therapy and preserve patients' quality of life, as well as improving patient overall survival.

5 Comparator

- 5.1 The submission nominated watchful waiting/placebo as the main comparator where 'watchful waiting' is in addition to ongoing ADT with or without the addition of secondary hormonal therapies (this is referred to as 'standard of care (SOC)'). The main arguments provided in support of this nomination were that there are currently no other PBS-funded treatment options available for the proposed patient population, and that watchful waiting was accepted by the PBAC as the main comparator for apalutamide. The ESC considered that SOC as the main comparator was appropriate.
- 5.2 The submission also nominated two near-market comparators, apalutamide and enzalutamide. The submission noted this was consistent with the apalutamide PSD

(paragraph 5.2, November 2018 apalutamide PSD). The ESC considered that the nomination of apalutamide and enzalutamide as near market comparators was appropriate.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (3), healthcare professionals (1) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described a range of perceived benefits of treatment with darolutamide including better tolerability compared with other treatments, delay of metastases, improvement in quality of life and extension of survival. The Geelong Prostate Support Group (PSG) supported the application to list darolutamide on the PBS for treatment of m0CRPC, noting the importance of effective treatments in the non-metastatic stage, and that results from the ARAMIS trial indicated that early intervention was effective. The Geelong PSG also considered that the potentially more tolerable side-effect profile of darolutamide compared to enzalutamide, due its reduced transport across the blood-brain barrier compared to existing treatments, would offer important quality of life improvements for patients. The Prostate Cancer Foundation of Australia also supported listing darolutamide on the PBS, noting there are currently few treatments for m0CRPC in Australia, and the results from the ARAMIS trial which indicate that darolutamide may extend metastases-free survival.

6.3 The Medical Oncology Group of Australia (MOGA) expressed its strong support for the darolutamide submission, categorising it as one of the therapies of “high priority for PBS listing” on the basis of the ARAMIS trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for darolutamide, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)¹, based on a comparison with placebo + ADT.

Clinical trials

6.4 The submission was based on the ARAMIS trial, a direct comparison of darolutamide and SOC in patients with m0CRPC at high risk of developing distant metastases, as well as two indirect comparisons versus the near market comparators apalutamide (using

¹ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017]

the SPARTAN trial) and enzalutamide (using the PROSPER trial), with SOC as the common reference. Details of the trials presented in the submission are provided in Table 3.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
ARAMIS	A multi-national, randomised, double blind, placebo-controlled, Phase III efficacy and safety study of darolutamide (ODM-201) in men with high risk non-metastatic-castration-resistant prostate cancer. Fizazi K, Shore N, Tammela TL, et al. Darolutamide in non-metastatic castration-resistant prostate cancer. Shore N, Zurth C, Fricke R, et al. Evaluation of clinically relevant drug-drug-interactions and population pharmacokinetics of darolutamide in patients with non-metastatic castration-resistant prostate cancer: Results of pre-specified and post hoc analyses of the Phase III ARAMIS trial.	February 2019 <i>NEJM</i> 2019; 380(13): 1235-1246 <i>Target Oncol</i> 2019; 14(5): 527-539
SPARTAN	Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. Small EJ, Saad F, Chowdhury S, et al. Apalutamide and overall survival in non-metastatic castration-resistant prostate cancer.	<i>NEJM</i> 2018; 378:1408-1418 <i>Ann Oncol</i> 2019; 30(11): 1813-1820
PROSPER	Hussain M, Fizazi K, Saad F, et al. Enzalutamide in men with non-metastatic, castration-resistant prostate cancer. Tombal B, Saad F, Penson D, et al. Patient-reported outcomes following enzalutamide or placebo in men with non-metastatic, castration-resistant prostate cancer (PROSPER): a multicentre, randomised, double-blind phase 3 trial.	<i>NEJM</i> 2018; 378(26): 2465-2474 <i>Lancet Oncol</i> 2019; 20(4): 556-569

Source: Table 2-6, p46 of the submission.

6.5 The key features of the included evidence and the comparisons made are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design	Risk of bias	Patient population	Outcomes	Comparisons
ARAMIS	Darolutamide: N=955 SOC: N=554 Total: N=1,509	R, DB, MC darolutamide+ ADT vs. SOC+ADT	Moderate	m0CRPC with high risk of distant metastases (PSADT ≤ 10 months)	Primary: MFS Secondary: OS, PFS, time to PSA progression, pain progression, first skeletal event, cytotoxic chemo, first use subsequent anti- neoplastic therapy	Direct comparison vs. SOC Indirect comparisons vs. apalutamide and vs. enzalutamide
SPARTAN	Apalutamide: N=806 SOC N=401 Total: N=1,207	R, DB, MC apalutamide+ ADT vs. SOC+ADT	Moderate		Primary: MFS Secondary: PFS, OS, time to PSA progression, symptomatic progression, cytotoxic chemo, metastasis	Indirect comparison vs. darolutamide
PROSPER	Enzalutamide: N=933 SOC: N=468 Total: N=1,401	R, DB, MC enzalutamide+ ADT vs. SOC+ADT	Moderate		Primary: MFS Secondary: OS, time to PSA progression, pain progression, first use subsequent anti-neoplastic therapy	Indirect comparison vs. darolutamide

Source: Table 2-7, p49 of the submission.

ADT=androgen deprivation therapy; chemo=chemotherapy; DB=double blind; MC=multi-centre; m0CRPC=non-metastatic castration resistant prostate cancer; MFS=metastasis-free survival; OS=overall survival; PSA=prostate specific antigen; R=randomised; PFS=progression-free survival; SOC=standard of care

- 6.6 The submission indicated that the risk of bias across the three trials was low. In its consideration of apalutamide in November 2018, the PBAC considered the risk of bias in SPARTAN was moderate due to the potential for unblinding based on the presence of prominent adverse events (AEs) such as skin rash (paragraphs 6.9 and 6.17, November 2018 PSD). AE data presented in the submission for ARAMIS demonstrated statistically significantly greater occurrence of AEs such as rash, fatigue and cardiovascular disorders with darolutamide compared to SOC. As such, there may be a similar potential for unblinding with darolutamide, and the PBAC considered the risk of bias was moderate.
- 6.7 Given only published articles were available for the PROSPER trial, the risk of bias cannot be accurately determined. However, based on the available information, the potential for risk of bias in PROSPER is likely to be no greater than the moderate risk of bias in ARAMIS and SPARTAN.
- 6.8 The submission concluded, based on subgroup analyses of the ARAMIS trial, that none of the baseline variables were likely to be treatment effect modifiers for either metastasis free survival (MFS) or overall survival (OS), and therefore, the indirect comparisons were not impacted by the differences across the trials for these variables. This conclusion differed from that made in the darolutamide application to Canadian

Agency for Drugs and Technologies in Health (CADTH²), where the sponsor had identified several treatment effect modifiers across the trials included in the indirect comparisons. The sponsor had stated that there were key fundamental design differences and heterogeneity among the ARAMIS, PROSPER and SPARTAN trials that could not be adjusted for analytically and the differences may make it difficult to compare the three trials included in the indirect comparisons (see paragraph 6.18).

Comparative effectiveness

- 6.9 Table 5 provides a summary of results for key time-to-event outcomes in ARAMIS. Some patients (5.2% in the darolutamide arm and 7.0% in the SOC arm) had been misclassified at baseline as not having metastases and analysis of the primary outcome (MFS) was provided correcting for this misclassification. The submission also provided interim and updated OS results. Additional analyses adjusting for crossover were provided (see Table 6).

²Available at:

https://www.cadth.ca/sites/default/files/pcodr/Reviews2020/10196DarolutamidenmCRPC_inCGR_REDACT_Post02Apr2020_final.pdf

Table 5: Summary of time-to-event outcomes in ARAMIS

Outcome	Interim analysis (17.9 months)		Updated analysis (29.1 months)	
	Darolutamide (N=955)	SOC (N=554)	Darolutamide (N=955)	SOC (N=554)
Metastasis-free survival (MFS)				
Event n (%)	221 (23.1%)	206 (39.0%)	Not reported	
Median months to metastasis (95% CI)	40.4 (34.3, NR)	18.4 (15.5, 22.3)		
HR (95% CI)	0.413 (0.341, 0.500)			
Metastasis-free survival (MFS) – censored (corrected for misclassification of patients)				
Event n (%)	171 (17.9%)	177 (31.9%)	Not reported	
Median months to metastasis (95% CI)	40.5 (35.8, NR)	22.1 (18.3, 25.8)		
HR (95% CI)	0.356 (0.29, 0.44)			
Overall survival (OS)				
Died n (%)	78 (8.2%)	58 (10.5%)	148 (15.5%)	106 (19.1%)
Median months to death (95% CI)	NE	NE	NE	NE
HR (95% CI)	0.706 (0.501, 0.994) ^a		0.685 (0.533, 0.881)	
Time to first symptomatic skeletal event (SSE)				
Event n (%)	16 (1.7%)	18 (3.2%)	29 (3.0%)	28 (5.1%)
Median months to SSE (95% CI)	NE	NE	NE	NE
HR (95% CI)	0.428 (0.218, 0.842) ^a		0.484 (0.287, 0.815) ^a	
Time to initiation of cytotoxic chemotherapy				
Event n (%)	73 (7.6%)	79 (14.3%)	127 (13.3%)	98 (17.7%)
Median months chemotherapy (95% CI)	NE	38.2 (22.4, 35.6)	NE	NE
HR (95% CI)	0.43 (0.31, 0.60) ^a		0.579 (0.444, 0.755) ^a	
Time to pain progression				
Event n (%)	251 (26.3%)	178 (32.1%)	Not reported	
Median months pain progression (95% CI)	40.3 (33.2, 41.2)	25.4 (19.1, 29.6)		
HR (95% CI)	0.65 (0.53, 0.79)			

Source: Table 2-18, p79 of the submission.

CI=confidence interval; HR=hazard ratio; MFS=metastasis-free survival; OS=overall survival; NE=not estimable; SOC=standard of care; **bold**=statistically significant

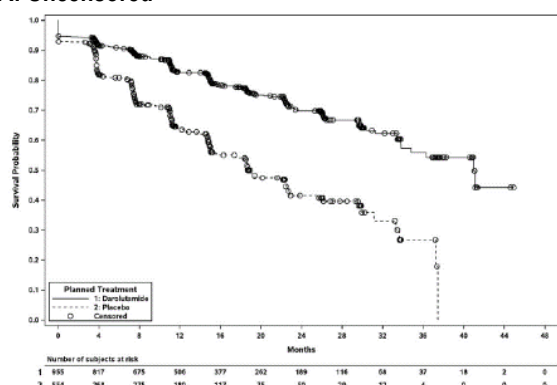
^a Not statistically significant given the pre-specified alpha significance level for the analysis was 0.0005.

6.10 The censored analysis of MFS, corrected for misclassification, showed a statistically significant improvement for darolutamide compared to SOC, demonstrating a 64% reduction in the risk of developing distant metastasis or death (HR=0.356; 95% CI: 0.29, 0.44). The median months to metastasis was approximately 18 months longer for darolutamide compared to SOC.

6.11 The Kaplan Meier plots for MFS, for both the uncensored and censored analyses (correcting for patient misclassification) are provided in Figure 1.

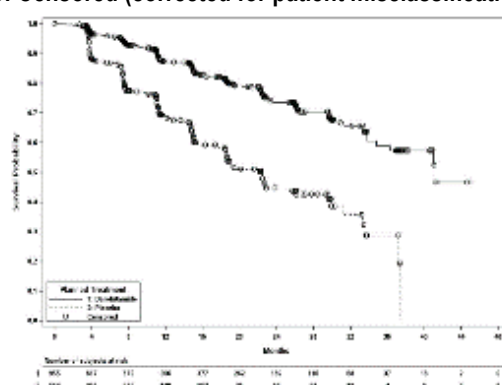
Figure 1: Kaplan Meier curves for MFS

A: Uncensored



Source: Figure 2.8, p75 of the submission.

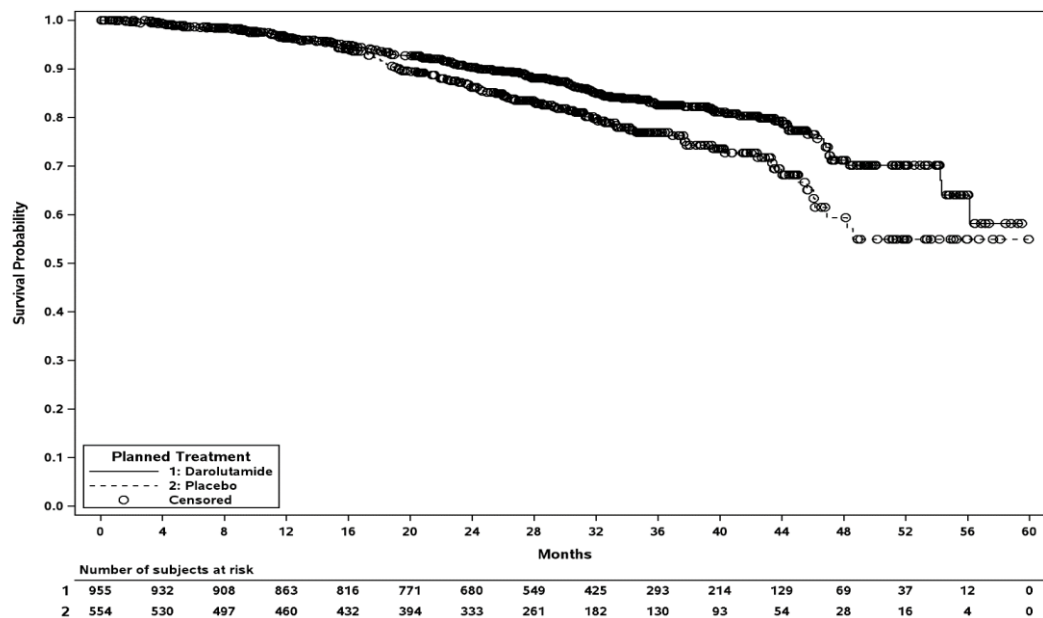
B: Censored (corrected for patient misclassification)



Source: Figure 2-32, p130 of the submission.

6.12 The ESC noted that the interim analysis for OS (median follow-up of 17.9 months) indicated no statistically significant advantage for darolutamide as the pre-specified alpha significance level of 0.0005 (to take into account alpha spent with multiple comparisons) was not met. In the updated analysis (median follow-up of 29.1 months) the planned number of events (240) was reached and the pre-specified significance level of 0.05 was met (HR=0.685; 95% CI: 0.533, 0.881; p=0.003). The Kaplan Meier plot for the updated analysis is provided in Figure 2.

Figure 2: Kaplan Meier curve for OS – updated analysis



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Source: Figure 2.11, p77 of the submission.

6.13 Patients in the SOC arm who experienced progression were allowed to crossover to the darolutamide arm. At the time of the updated analysis, 170/554 SOC-treated

patients (30.7%) had crossed over. To account for potential confounding, the submission provided adjusted analyses, using iterative parameter estimation (IPE) and rank preserving structural failure time (RPSFT) analyses. Results for the crossover adjusted analyses are provided in Table 6.

Table 6: Crossover adjusted OS analyses in ARAMIS

	Darolutamide (N=955)	SOC (N=554)
IPE (median follow-up 29.1 months)		
Died n (%)	148 (15.5%)	106 (19.1%)
Median months to death (95% CI)	██████████	██████████
HR (95% CI)	██████████	██████████
RPSFT (median follow-up 29.1 months)		
Died n (%)	148 (15.5%)	██████████
Median months to death (95% CI)	██████████	██████████
HR (95% CI)	██████████	██████████

Source, Table 1, p4 of Appendix A of the submission.

CI=confidence interval; HR=hazard ratio; IPE=iterative parameter estimation; OS=overall survival; NE=not estimable; RPSFT=rank preserving structural failure time; SOC=standard of care; bold=statistically significant

- 6.14 The crossover adjusted analyses using IPE, showed a █████% reduction in the risk of death (HR=█████; 95% CI: █████, █████), a slightly larger reduction compared to the unadjusted updated analysis (31.5%, HR=0.685; 95% CI: 0.533, 0.881). The RPSFT analysis showed a █████% reduction in the risk of death, similar to that for the unadjusted updated analysis. In the economic model the submission applied the unadjusted updated OS data in the base case, with crossover adjusted data used in sensitivity analyses.
- 6.15 For patient-reported outcomes, while there were statistically significant differences reported for some scales (BPI-SF, EORTC), these differences were not clinically meaningful, as the differences did not reach the minimally important difference thresholds. There were no statistically significant, or clinically meaningful, differences between darolutamide and SOC observed for the EQ-5D. The submission concluded that the results for the quality of life (QoL) outcomes implied that QoL was maintained while on treatment. The results also demonstrate that over the trial follow-up period darolutamide treatment did not improve the QoL of patients.
- 6.16 The results of the indirect comparisons versus apalutamide and enzalutamide are provided in Table 7.

Table 7: Results of indirect comparisons for darolutamide vs. apalutamide and darolutamide vs. enzalutamide – MFS and OS

Trial/comparison	Outcome	Active trt n/N (%)	SOC n/N (%)	HR (95% CI)
MFS (not corrected for misclassification of patients in ARAMIS)				
ARAMIS: darolutamide (17.9 months median follow-up)	Events	221/955 (23.1%)	206/554 (39.0%)	
	Median months MFS	40.4	18.4	0.413 (0.341, 0.500)
SPARTAN: apalutamide (20.3 months median follow-up)	Events	184/806 (22.8%)	228/401 (48.7%)	-
	Median months MFS	40.5	14.7	0.28 (0.23, 0.35)
PROSPER: enzalutamide (18.5 months ^a median follow-up)	Events	219/933 (23.5%)	228/468 (48.7%)	-
	Median months MFS	36.6	14.7	0.29 (0.24, 0.35)
indirect comparison darolutamide vs. apalutamide				1.475 (1.11, 1.96)
indirect comparison darolutamide vs. enzalutamide				1.424 (1.089, 1.863)
MFS (corrected for misclassification of patients in ARAMIS)				
ARAMIS: darolutamide (29.1 months median follow-up)	Events	171 (17.9%)	177 (31.9%)	-
	Median months MFS	40.5	22.1	0.356 (0.287, 0.441)
SPARTAN: apalutamide (20.3 months median follow-up)	Events	184/806 (22.8%)	228/401 (48.7%)	-
	Median months MFS	40.5	14.7	0.28 (0.23, 0.35)
PROSPER: enzalutamide (18.5 months ^a median follow-up)	Events	219/933 (23.5%)	228/468 (48.7%)	-
	Median months MFS	36.6	14.7	0.29 (0.24, 0.35)
indirect comparison darolutamide vs. apalutamide				1.271 (0.942, 1.717)
indirect comparison darolutamide vs. enzalutamide				1.228 (0.922, 1.634)
OS (updated)				
ARAMIS: darolutamide (29.1 months median follow-up)	Dead	148/955 (15.5%)	106/554 (19.1%)	-
	Median months OS	NE	NE	0.685 (0.533, 0.881)
SPARTAN: apalutamide (41.0 months median follow-up)	Dead	178/806 (22.1%)	107/401 (26.7%)	-
	Median months OS	NE	NE	0.75 (0.59, 0.96)
PROSPER: enzalutamide (NR median follow-up)	Dead	NR	NR	-
	Median months OS	NR	NR	0.83 (0.65, 1.06)
indirect comparison darolutamide vs. apalutamide				0.913 (0.644, 1.296)
indirect comparison darolutamide vs. enzalutamide				0.825 (0.581, 1.172)

Source: Table 2-18, p79; Table 2-20, p84; Table 2-21, p87; Table 2-32, p128; Table 2-33, p131 of the submission.

CI=confidence interval; HR=hazard ratio; MFS=metastasis-free survival; OS=overall survival; NE=not estimable; NR=not reported; SOC=standard of care; trt=treatment; **bold**=statistically significant

^a Median-follow-up for the SOC arm in PROSPER was 15.1 months

6.17 The indirect comparisons of OS resulted in no statistically significant differences between darolutamide and apalutamide or between darolutamide and enzalutamide. The indirect comparisons of MFS (not corrected) resulted in a statistically significant advantage for both apalutamide and enzalutamide when compared to darolutamide. However, when the MFS comparisons were performed correcting for the misclassification of ARAMIS patients who had baseline metastases, the differences were not statistically significant. The submission argued that the inclusion of patients with metastases at baseline resulted in an underestimation of the darolutamide treatment effect.

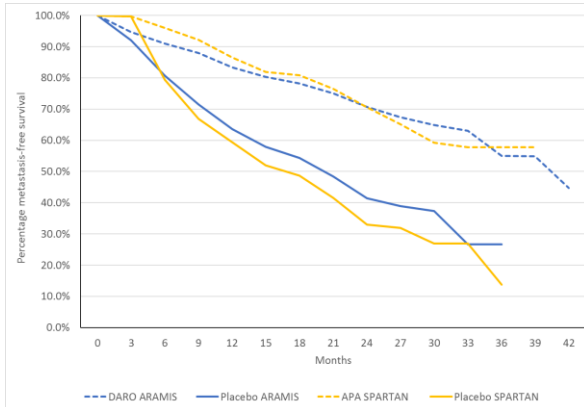
6.18 In the CADTH application the sponsor had stated that given the heterogeneity among the trials that could not be adjusted for (i.e., the difference in number of patients who initiated new anti-cancer therapy prior to metastasis in ARAMIS, PSA being unblinded in ARAMIS, patients with metastasis at baseline, treatment effect modifiers, patients

with a history of seizures), the comparative estimates from indirect comparisons should be considered unreliable.

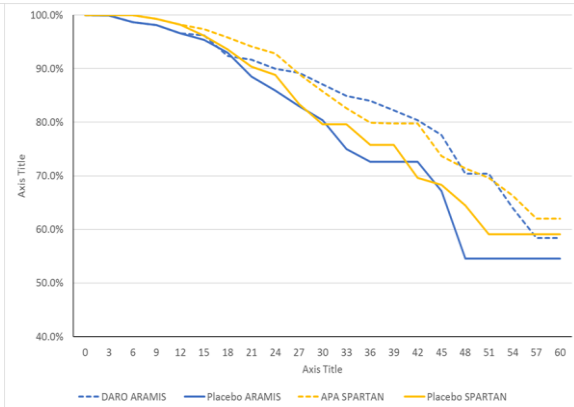
6.19 The submission provided an overlay of the MFS and OS curves from ARAMIS (darolutamide) and SPARTAN (apalutamide) trials (Figure 3).

Figure 3: Overlay of MFS and OS curves from ARAMIS and SPARTAN

A: MFS



B: OS



Source: Figure 2-31, p129 of the submission.

Source: Figure 2-32, p130 of the submission.

6.20 While the MFS and OS curves are reasonably similar for the active treatment arms in both trials, the placebo arms appeared to be less similar, particularly for MFS. This suggests patient differences between the trials, which had been noted by the CADTH application (see paragraph 6.18).

Comparative harms

6.21 Table 8 provides a summary of AEs of special interest in the ARAMIS trial. These were defined as events/disorders representing potential or known risks associated with ADT or second-generation androgen receptor inhibitors, such as fracture, fall, seizure, rash, cardiovascular disorders and other events.

Table 8: Summary of adverse events of special interest in ARAMIS

	DARO, n (%) (N=954)	SOC, N (%) (N=554)	RR (95% CI)	RD (95% CI)	Exposure-adjusted incidence rate per 100 patient years		
					DARO	SOC	Risk ratio
Bone fracture	40 (4.2%)	20 (3.6%)	1.16 (0.69, 1.97)	0.01 (-0.01, 0.03)	3.0	3.5	0.9
Fall	40 (4.2%)	26 (4.7%)	0.89 (0.55, 1.45)	-0.01 (-0.03, 0.02)	3.0	4.6	0.7
Fatigue/ asthenia	151 (15.8%)	63 (11.4%)	1.39 (1.06, 1.83)	0.04 (0.01, 0.08)	11.3	11.1	1.0
Weight decreased	34 (3.6%)	12 (2.2%)	1.65 (0.86, 3.15)	0.01 (0.00, 0.03)	2.5	2.1	1.2
Seizure	2 (0.2%)	1 (0.2%)	1.16 (0.11, 12.78)	0.00 (0.00, 0.00)	0.1	0.2	0.5
Rash	28 (2.9%)	5 (0.9%)	3.25 (1.26, 8.37)	0.02 (0.01, 0.04)	2.1	0.9	2.3
Cardiovascular disorders	113 (11.8%)	41 (7.4%)	1.60 (1.14, 2.25)	0.04 (0.01, 0.08)	NA	NA	NA
CNS vascular disorders	16 (1.7%)	10 (1.8%)	0.93 (0.42, 2.03)	0.00 (-0.01, 0.01)	1.2	1.7	0.7
Hypertension	70 (7.3%)	33 (6.0%)	1.23 (0.83, 1.84)	0.01 (-0.01, 0.04)	5.2	5.8	0.9
Vasodilatation and flushing	54 (5.7%)	23 (4.2%)	1.36 (0.85, 2.20)	0.02 (-0.01, 0.04)	4.0	4.1	1.0
Diabetes and hyperglycaemia	22 (2.3%)	12 (2.2%)	1.06 (0.53, 2.13)	0.00 (-0.01, 0.02)	1.6	2.1	0.8
Mental-impairment disorders	16 (1.7%)	10 (1.8%)	0.93 (0.42, 2.03)	0.00 (-0.01, 0.01)	1.2	1.7	0.7
Depressed mood disorders	17 (1.8%)	8 (1.4%)	1.23 (0.54, 2.84)	0.00 (-0.01, 0.02)	1.3	1.4	0.9
Breast disorders/ gynaecomastia	22 (2.3%)	9 (1.6%)	1.42 (0.66, 3.06)	0.01 (-0.01, 0.02)	1.6	1.6	1.0

Source: Table 2-25, p99-100 of the submission.

DARO=darolutamide; confidence interval; NA=not available; RD=risk difference; RR=relative risk; SOC=standard of care

- 6.22 In ARAMIS, an increased risk of rash, fatigue and cardiovascular disorders was associated with darolutamide treatment compared to SOC.
- 6.23 The Pharmaceutical Safety and Efficacy Assessment (PSEAT) from Health Canada for darolutamide stated that "...these data may suggest that the addition of darolutamide to ADT increases the severity of coronary artery disorder events. While the signal may not be sufficient to warrant inclusion text with the Warnings and Precautions section of the PM, additional labelling should be considered. A further signal could be detected upon continued exposure in the post-market setting, and the data will be brought to the attention of the RMP reviewer". The Pre-Sub-Committee Response (PSCR) noted there was a higher proportion of patients with a medical history of cardiac disorders at baseline in the darolutamide + ADT arm (46.1%) compared to the ADT arm (40.3%) and that these patients represented the majority who experienced coronary artery disorder or heart failure treatment emergent AEs (TEAEs) in both treatment arms. The PSCR also noted that there was no significant difference between the darolutamide + ADT and ADT arms for any cardiac disorder related TEAE when incidence rates were adjusted for exposure. The PSCR considered that overall, darolutamide was not found to increase the risk of cardiovascular disorders, compared to ADT alone. The ESC considered that post-market monitoring would be important to discern whether there are additional safety signals for cardiac events with darolutamide.

Benefits/harms

6.24 A summary of the comparative benefits and harms for darolutamide versus SOC is presented in Table 9.

Table 9: Summary of comparative benefits and harms for darolutamide and SOC

Benefits						
Metastasis-free survival (median follow-up 17.9 months); not censored/corrected for misclassification of patients with metastases at baseline						
ARAMIS	Darolutamide N=955	SOC N=554	Absolute difference	HR (95% CI)		
Event n (%)	221 (23.1%)	206 (39.0%)	-	0.413 (0.341, 0.500)		
% metastasis-free (95% CI)	76.9% (NR)	61.0% (NR)	15.9			
Median months to metastasis (95% CI)	40.4 (34.3, NR)	18.4 (15.5, 22.3)	22.0			
% metastasis-free at 12 months (95% CI)	82.5% (79.9, 85.1)	63.5% (58.8, 68.1)	19.0			
% metastasis-free at 24 months (95% CI)	69.8% (65.8, 73.8)	41.5% (35.1, 48.0)	28.3			
% metastasis-free at 36 months (95% CI)	54.3% (46.6, 62.0)	26.8% (16.0, 37.5)	27.5			
Overall survival (median follow-up 29.1 months; not adjusted for crossover)						
Died n (%)	148 (15.5%)	106 (19.1%)	-	0.685 (0.533, 0.881)		
% alive (95% CI)	84.5% (NR)	80.9% (NR)	3.6			
Median months to death (95% CI)	NE	NE	-			
% alive at 12 months (95% CI)	96.3% (95.1, 97.5)	96.4% (94.8, 98.1)	-0.1			
% alive at 24 months (95% CI)	90.3% (88.3, 92.3)	86.2% (83.0, 89.4)	4.1			
% alive at 36 months (95% CI)	82.6% (79.6, 85.5)	76.9% (72.4, 81.4)	5.7			
Harms						
ARAMIS	Darolutamide N=955	SOC N=554	RR (95% CI)	Events/100 patients^a		RD (95% CI)
				Darolutamide	SOC	
Cardiovascular disorders	113 (11.8%)	41 (7.4%)	1.60 (1.14, 2.25)	12	7	0.04 (0.01, 0.08)
Rash	28 (2.9%)	5 (0.9%)	3.25 (1.26, 8.37)	3	1	0.02 (0.01, 0.04)
Fatigue/ asthenia	151 (15.8%)	63 (11.4%)	1.39 (1.06, 1.83)	16	11	0.04 (0.01, 0.08)

Source: Table 2-18, p79; Table 2-25, p99-100 of the submission; Table 9.2, p74 of the ARAMIS CSR; Table 14.2.2, p1 of the ARAMIS – final – efficacy-Table 14_ provided with the submission.

CI=confidence interval; HR=hazard ratio; NE=not estimable; NR=not reported; RD=risk difference; RR=relative risk; SOC=standard of care; **bold**=statistically significant

6.25 On the basis of direct evidence presented by the submission, for every 100 patients treated with darolutamide in comparison with SOC:

- Approximately 19 additional patients will remain metastasis-free after 12 months
- Approximately 28 additional patients will remain metastasis-free after 24 months and after 36 months
- Approximately 4 additional patients will remain alive after 24 months
- Approximately 6 additional patients will remain alive after 36 months
- After 18 months, approximately 4 additional patients would experience cardiovascular disorders, 2 additional patients would experience rash, and 4 additional patients would experience fatigue.

Clinical claim

6.26 The submission made the following clinical claims regarding darolutamide:

- Superior effectiveness and inferior safety compared to SOC;
 - Non-inferior effectiveness and superior safety compared to apalutamide;
 - Non-inferior effectiveness and superior safety compared to enzalutamide.
- 6.27 The ESC noted that darolutamide demonstrated a statistically significant advantage in MFS compared to SOC. Although the updated analysis of OS (median follow-up of 29.1 months) also demonstrated a statistically significant benefit for darolutamide compared to SOC, the ESC considered that there was some uncertainty as to the magnitude of benefit as median OS was not reached in either treatment arm.
- 6.28 With regard to safety, the ESC noted that the ARAMIS trial resulted in statistically significantly greater occurrences of rash, fatigue and cardiovascular disorders with darolutamide treatment compared to SOC.
- 6.29 The PBAC considered that the clinical claims that darolutamide resulted in superior efficacy and inferior safety compared to SOC were adequately supported by the evidence presented. The PBAC considered that due to the immaturity of the overall survival data, the magnitude of the survival benefit was uncertain.
- 6.30 Although noting the limitations of the indirect comparisons (paragraph 6.18), the PBAC considered that overall, the efficacy of darolutamide would likely be non-inferior compared to apalutamide and enzalutamide. The PBAC considered that darolutamide may be better tolerated compared to apalutamide and enzalutamide due to its reduced penetration of the blood-brain barrier which could potentially result in less central nervous system toxicity.

Economic analysis

- 6.31 The submission presented a stepped economic evaluation based on the ARAMIS trial, comparing darolutamide to SOC. A cost-utility analysis using a partitioned survival model with three health states was provided. Table 10 provides a summary of model inputs.

Table 10: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Darolutamide vs. SOC
Time horizon	10 years in the model base case versus 4 years in ARAMIS
Outcomes	QALYs; LYs
Methods used to generate results	Partitioned survival model
Health states	Three health states: - m0CRPC; metastatic free: Based on MFS data from ARAMIS - mCRPC; metastatic progressed: Based on OS data from ARAMIS - dead
Cycle length	28 days, half cycle correction applied
Allocation to health states	Health state allocation determined by MFS and OS curves, which were based on ARAMIS data with extrapolation
Extrapolation	MFS (m0CRPC) Trial-based Kaplan Meier curves: 0-36 months Extrapolation: exponential 37-120 months
	OS (mCRPC) Trial-based Kaplan Meier curves: 0-44 months Extrapolation: Weibull 37-120 months
	TTD (darolutamide treatment) Trial-based Kaplan Meier curves: 0-44 months Extrapolation: Gompertz 37-120 months
	Time to subsequent therapy Trial-based Kaplan Meier curves: 0-44 months Extrapolation: log-normal 37-120 months
Health related quality of life	m0CRPC: ██████ for darolutamide and ██████ for SOC sourced from ARAMIS. mCRPC: ██████ (ALSYMPCA trial sourced from literature)
Subsequent therapy	Darolutamide-treated patients could receive only docetaxel and cabazitaxel, while SOC-treated patients could receive docetaxel, cabazitaxel, abiraterone and enzalutamide as subsequent treatments in the model.

Source: Table 3-1, p187; Table 3-9, p215 of the submission

m0CRPC=non-metastatic castration resistant prostate cancer; mCRPC=metastatic castration resistant prostate cancer; MFS=metastasis-free survival; SOC=standard of care; TTD=time to treatment discontinuation

- 6.32 The model is structurally similar to the apalutamide model considered by the PBAC in July 2019. The darolutamide submission adopted the adjustments advised by the PBAC in regard to the July 2019 apalutamide model – use of blinded independent central review MFS, a 10-year time horizon and OS results that have not been adjusted for treatment switching (paragraph 7.13, July 2019 apalutamide PSD).
- 6.33 The submission stated that to account for the effect of restricting subsequent apalutamide and enzalutamide use in the darolutamide arm, the base case of the model applied the cost of docetaxel and cabazitaxel for these patients, while SOC-treated patients received docetaxel, cabazitaxel, abiraterone and enzalutamide as subsequent treatments in the model. The PBAC noted that this corresponded to previous advice in regard to the requested listing for apalutamide (paragraphs 7.3 and 7.4, July 2019 apalutamide PSD).
- 6.34 A summary of the key drivers of the economic model is provided in Table 11.

Table 11: Key drivers of the model

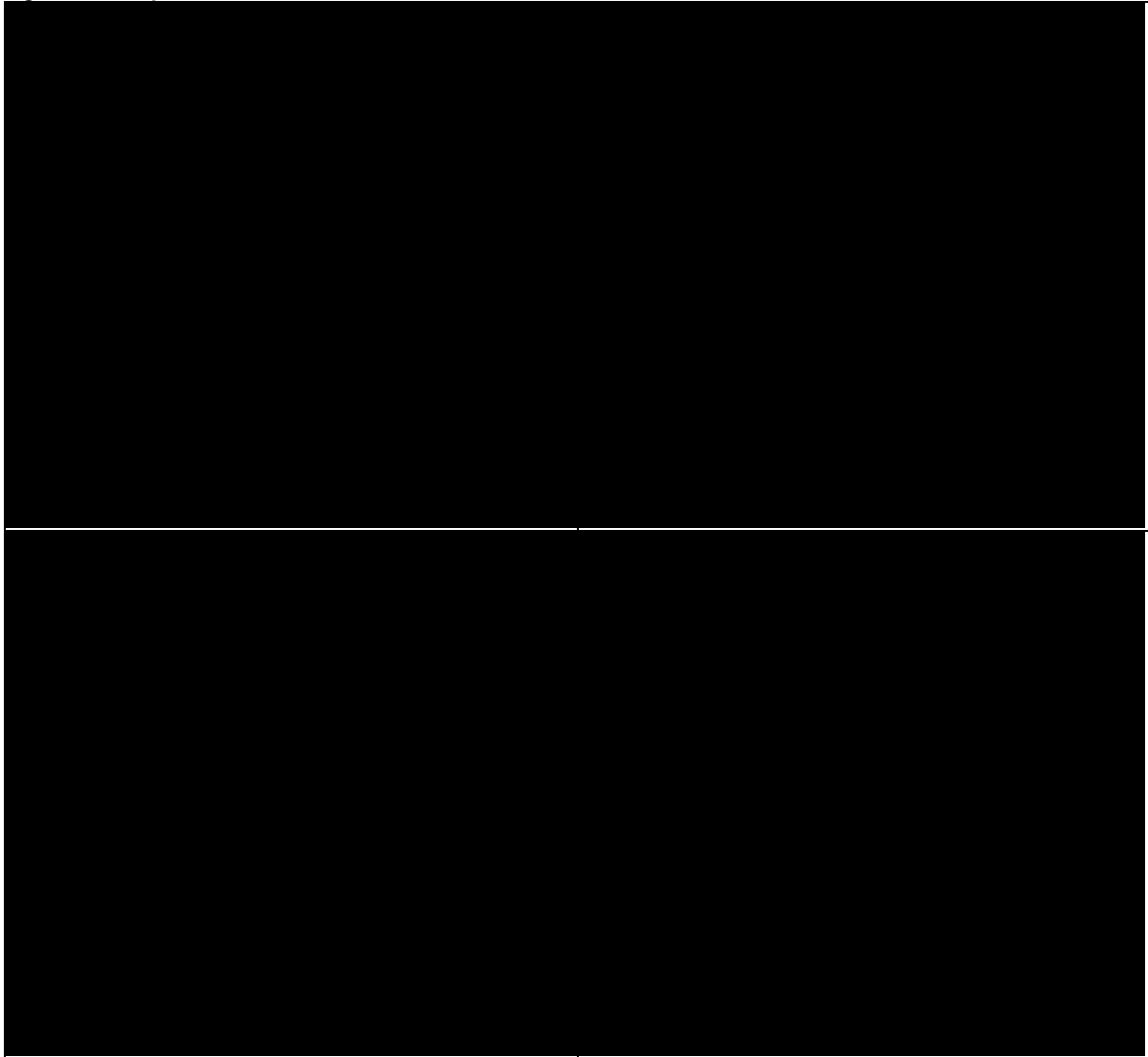
Description	Method/Value	Impact
Utilities	The value of █████ for patients in the metastatic state was considerably lower than the values used in the m0CRPC state (█████ for darolutamide; █████ for SOC). The model demonstrated high sensitivity to the m0CRPC utility value.	High, favours darolutamide
Extrapolation	For MFS, the exponential curve was selected for use in the base case. The submission indicated that the exponential and Gompertz models were the best fitting. For OS, the submission elected to use the Weibull function to extrapolate results beyond the trial, stating that it was the most conservative of the best-fitting models (which also included the log-logistic and Gompertz functions). The model showed sensitivity to all identified best-fitting curves and contrary to the submission's claim, for OS, the Gompertz model was the most conservative (see Figure 4 below).	High, favours darolutamide

Source: Section 3.4 to Section 3.5, p200-225 of the submission.

m0CRPC=non-metastatic castration resistant prostate cancer; MFS=metastasis-free survival; OS=overall survival; SOC=standard of care

6.35 Figure 4 illustrates extrapolations of MFS and OS in the model.

Figure 4: Extrapolations of MFS and OS in the model



Source: Worksheet 'MFS' of the Excel workbook 'DARO_Section3Model_March2020 FINAL'.
KM=Kaplan Meier; MFS=metastasis-free survival; SOC=standard of care

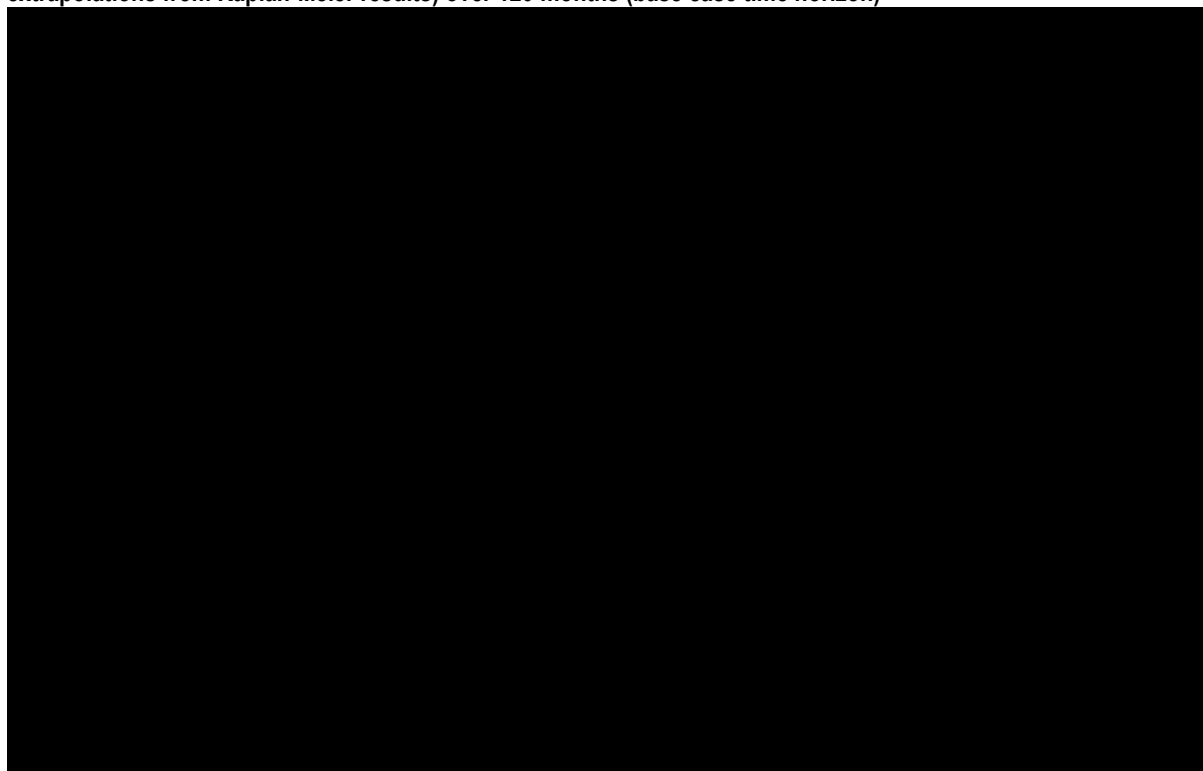
6.36 Based on visual inspection of the MFS curves in both the darolutamide and SOC arms, the Gompertz and the exponential functions appeared the best fit versus the Kaplan Meier data. The submission applied the exponential function. The generalised gamma function also demonstrated good fit for the SOC arm but not for the darolutamide arm, where divergence from the Kaplan Meier curve was evident from approximately 24 months. In this regard, visual goodness of fit appear to contravene the reported Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values for darolutamide, as the AIC and BIC values suggested that the generalised gamma function gave the best overall fit of the data. The PSCR noted that extrapolation and fitting of MFS curves was complicated by a small number of patients who had metastases at baseline. This resulted in lower AIC/BIC values for parametric functions

with early steep declines. The PSCR stated that the exponential function was selected based on both visual inspection and AIC/BIC statistics. The ESC considered that while the approach used by the submission to select the parametric function for MFS seemed reasonable, the most appropriate extrapolation method for MFS would need to be congruent with the extrapolation of OS, and both the MFS and OS extrapolations would need to be clinically plausible in the context of the course of the disease.

6.37 For OS, while all parametric functions illustrated reasonable fit to the Kaplan Meier data, beyond 36 months the curves diverged. Contrary to the submission’s claim that Weibull extrapolations produce the most conservative estimates in the model, the results suggest that Gompertz extrapolations were more conservative, with a more rapid decline in survival beyond 48 months predicted for both darolutamide and SOC. The PSCR noted that selection of the Gompertz function was inappropriate as it results in an artificial and clinically implausible truncation of the MFS curves and 100% mortality with 8 years for patients in the SOC arm (see Figure 6 and paragraph 6.40).

6.38 Figure 5 compares the modelled MFS and OS with that from the trial.

Figure 5: Trial based MFS and OS (as illustrated by the Kaplan Meier curves) versus modelled results (based on extrapolations from Kaplan-Meier results) over 120 months (base case time horizon)



DARO=darolutamide KM=Kaplan Meier; PBO=placebo

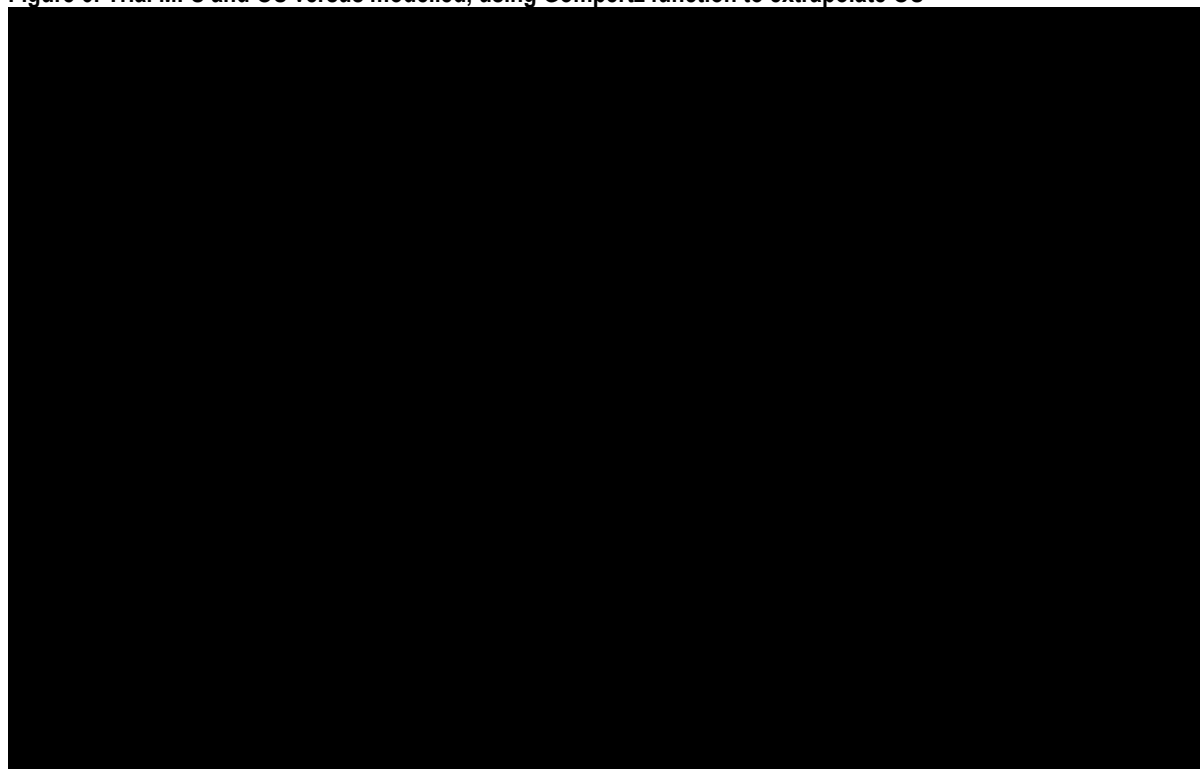
Source: constructed during the evaluation based on information presented in the Excel workbook 'DARO_Section3Model_March2020 FINAL'

6.39 Figure 5 illustrates that in the base case analysis, the results for both MFS and OS were informed mostly by extrapolated rather than within trial data. The ESC noted that

approximately █% of patients treated with darolutamide were predicted to be alive at 10 years (120 months), with █% not experiencing progression. In contrast, for SOC-treated patients (placebo-treated in Figure 5) only █% were estimated to be alive at 10 years. The ESC also noted that the modelled MFS and OS curves did not converge at the end of the time horizon. The ESC considered that, given the average age of the population (73.6 years at the beginning of the model), a significant portion of patients would likely die without metastatic disease. The pre-PBAC Response noted that the MFS and OS curves did converge outside of the 10 year time horizon and non-cancer related mortality was accounted for in the model. The PBAC noted that the MFS and OS curves converged at approximately █ years.

- 6.40 The results were largely influenced by the choice of parametric survival functions. As illustrated by Figure 6, when the OS extrapolations were assumed to follow the Gompertz function rather than Weibull (as was in the base case), the model predicted that all patients would have died by 10 years and the extrapolated MFS curves for darolutamide and SOC (placebo) would be truncated due to the reduced OS. Application of the Gompertz function resulted in an incremental cost-effectiveness ratio (ICER) of \$45,000/QALY - \$75,000/QALY, compared to \$45,000/QALY - \$75,000/QALY in the base case (Weibull function). The PSCR noted that application of the Gompertz function for OS extrapolation in the darolutamide arm requires an artificial truncation of the corresponding MFS curve which results in all patients free of metastatic disease at approximately 80 months, dying within the following 40 months. The PSCR also noted that application of the Gompertz curve to OS in the SOC arm, results in all patients dying within 8 years. On this basis, the ESC considered that application of the Gompertz function to OS may underestimate OS for SOC.

Figure 6: Trial MFS and OS versus modelled, using Gompertz function to extrapolate OS



DARO=darolutamide KM=Kaplan Meier; PBO=placebo

Source: constructed during the evaluation based on information presented in the Excel workbook 'DARO_Section3Model_March2020 FINAL'

6.41 The results of the economic evaluation are provided in Table 12. The submission noted that an effective price for enzalutamide and abiraterone have been assumed based on the effective price of enzalutamide provided to the sponsor as part of the listing of radium 223, while the price used for cabazitaxel was the published price.

Table 12: Results of the stepped economic evaluation

Step and component	Darolutamide	SOC	Increment
Step 1: trial-based time horizon (4 years)			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
MFS year	[REDACTED]	[REDACTED]	0.83
LY	[REDACTED]	[REDACTED]	0.14
QALY	[REDACTED]	[REDACTED]	0.34
Incremental cost/MFS year gained	[REDACTED]	[REDACTED]	\$ [REDACTED]
Incremental cost/extra LY gained	[REDACTED]	[REDACTED]	\$ [REDACTED]
Incremental cost/extra QALY gained	[REDACTED]	[REDACTED]	\$ [REDACTED]
Step 2: 10 year time horizon			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LY	[REDACTED]	[REDACTED]	0.94
Incremental cost/extra LY gained (base case)	[REDACTED]	[REDACTED]	\$ [REDACTED]
QALY	[REDACTED]	[REDACTED]	1.05
Incremental cost/extra QALY gained (base case)	[REDACTED]	[REDACTED]	\$ [REDACTED]

Source: Table 3-30, p247; Table 3-33, p248 of the submission and the 'Model Results' worksheet of the Excel workbook 'DARO_Section3Model_March2020 FINAL'.

MFS=metastasis-free survival; SOC=standard of care

The redacted table shows ICERs in the range of \$45,000/QALY - \$75,000/QALY.

- 6.42 The gains in incremental life years and QALYs over the 4-year trial-based time horizon were 0.14 and 0.34 respectively. Thus, the majority of the total estimated life year and QALY gains (0.94 and 1.05 respectively) were in the extrapolated period. The QALY gain (1.05) was greater than the life years gained (0.94), which reflected the considerable difference in utilities assigned to the metastatic castration resistant prostate cancer (mCRPC; [REDACTED]) and mOCRPC ([REDACTED] for darolutamide; [REDACTED] for SOC) health states. The ESC considered that the same utility value should be applied to all patients in the mOCRPC health state.
- 6.43 With regards to the July 2019 apalutamide model, the PBAC considered that an ICER in the range of \$40,000 to \$45,000 per QALY would be required (paragraph 7.17, July 2019 apalutamide PSD). The submission noted that the darolutamide model incorporated advice from the PBAC regarding the apalutamide model (blinded independent review, 10-year time horizon, no adjustment for treatment switching in OS) and stated that the clinical evidence for darolutamide demonstrated an OS benefit. The submission concluded that if an ICER of between \$40,000 and \$45,000 per QALY was considered reasonable for apalutamide in the absence of a demonstrated OS benefit, then all else equal, an ICER of approximately \$45,000/QALY - \$75,000/QALY with a demonstrated OS benefit was reasonable. While there was a statistically significant OS advantage for darolutamide, the ESC noted that there was some uncertainty in the magnitude of benefit given that the trial evidence was immature as median OS had not been reached in either arm.
- 6.44 Sensitivity analyses indicated that the model was sensitive to extrapolation of the survival curves and the utility value for the mCRPC health state; the results of key sensitivity analyses are summarised in Table 13.

Table 13: Results of sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER	% change ICER
Base case	\$ [REDACTED]	1.05	\$ [REDACTED]	-
OS data (base case: not adjusted for treatment switching)				
Adjusted for treatment switching (IPE)	\$ [REDACTED]	1.13	\$ [REDACTED]	-7.3%
MFS and OS extrapolation (base case: MS: exponential; OS: Weibull)				
MFS gamma; OS log-logistic	\$ [REDACTED]	1.18	\$ [REDACTED]	-10.6%
MFS Gompertz; OS Gompertz	\$ [REDACTED]	0.88	\$ [REDACTED]	+27.8%
MFS: exponential; OS: Gompertz	\$ [REDACTED]	0.87	\$ [REDACTED]	+29.4%
mCRPC health state utility (base case: [REDACTED])				
Increase [REDACTED] by 20% to [REDACTED]	\$ [REDACTED]	0.95	\$ [REDACTED]	+10.0%
[REDACTED] trial-based - ARAMIS	\$ [REDACTED]	0.83	\$ [REDACTED]	+25.6%
0.70 - TRAPEZE	\$ [REDACTED]	0.89	\$ [REDACTED]	+17.1%
Time horizon (base case: 10 years)				
5 years	\$ [REDACTED]	0.46	\$ [REDACTED]	+122.2%
15 years	\$ [REDACTED]	1.33	\$ [REDACTED]	-16.1%
Multivariate analysis				
mCRPC utility and MFS extrapolation (base case: [REDACTED] and exponential)				
0.70 and gamma	\$ [REDACTED]	0.97	\$ [REDACTED]	+8.4%
mCRPC utility and OS extrapolation (base case: [REDACTED] and Weibull)				
0.70 and log-logistic	\$ [REDACTED]	0.80	\$ [REDACTED]	+30.2%
mCRPC utility with MFS; OS extrapolation (base case: [REDACTED] and MFS exponential; OS Weibull)				
0.70 and MFS exponential; OS Gompertz	\$ [REDACTED]	0.71	\$ [REDACTED]	+58.1%
0.70 and MFS gamma; OS log-logistic	\$ [REDACTED]	0.88	\$ [REDACTED]	+19.4%
0.70 and MFS Gompertz; OS Gompertz	\$ [REDACTED]	0.72	\$ [REDACTED]	+57.1%
mCRPC utility and OS data (base case: [REDACTED] and OS data unadjusted)				
0.70 and OS data adjusted (IPE)	\$ [REDACTED]	1.01	\$ [REDACTED]	+4.3%
mCRPC utility and cost of terminal care (base case [REDACTED] and \$ [REDACTED])				
0.70 and \$ [REDACTED]	\$ [REDACTED]	0.89	\$ [REDACTED]	+25.3%

Source: Table 3-34, p250-252 of the submission.

m0CRPC=non-metastatic castration resistant prostate cancer; mCRPC=metastatic castration resistant prostate cancer; MFS=metastasis-free survival; OS=overall survival

The redacted table shows ICERs in the range of \$45,000/QALY - \$200,000/QALY.

6.45 The ESC noted that use of the trial-based utility value for mCRPC patients from ARAMIS ([REDACTED]), rather than the value used in the model of [REDACTED] from the ALSYMPCA trial, increased the ICER by approximately 25% to \$45,000/QALY - \$75,000/QALY. The submission argued the ARAMIS utility value was unlikely to represent mCRPC patients over time, as it was collected in patients who had recently been diagnosed with progressed disease. Another value sourced by the submission from the literature (0.70 from TRAPEZE) resulted in a 17% increase in the ICER, to \$45,000/QALY - \$75,000/QALY. This value was applied in multivariate analyses performed during the evaluation. The PSCR contended that the utility value of [REDACTED] was more representative of patients in the mCRPC health state as the ALSYMPCA trial did not restrict prior use of cytotoxic chemotherapy and as patients had two or more bone metastases at baseline. The PSCR noted that 80% to 90% of patients with advanced-stage prostate cancer develop bone metastases during the disease course. The PSCR further argued that the utility value of 0.70 from the TRAPEZE trial was unlikely to capture all effects associated with mCRPC and this value was not consistent with

values reported in the literature for late stage prostate cancer which ranged from 0.45 to 0.55. While the ESC acknowledged that the utility value for patients with mCRPC would reduce over time, the ESC considered that the utility value of [REDACTED] was more reflective of end stage palliation and was therefore unlikely to reflect a patient's utility throughout their entire time in the mCRPC health state given patients may remain in this health state for several years. The ESC considered that the utility value of 0.635 sourced from Wu et al. 2007³, which was based on multicentre observational data of patients with metastatic hormone-refractory prostate cancer over two years, may be an appropriate alternative value for the mCRPC health state and may be more reflective of the total time spent in the mCRPC state. The pre-PBAC Response maintained that the utility value of [REDACTED] best reflected quality of life over the total time spent in the mCRPC health state. The pre-PBAC Response noted that the utility value of 0.635 from Wu et al. 2007 was the baseline utility value for patients in the multicentre observational study and that the 3-month and 9-month utility values from the study were 0.565 and 0.555 respectively, which are similar to the value for the mCRPC health state in the base-case.

- 6.46 The model was sensitive to the choice of extrapolation functions for OS and MFS. A univariate sensitivity analysis using the Gompertz function (a model with visibly good fit for the Kaplan Meier OS data, but more conservative than the Weibull model) to extrapolate OS resulted in an ICER of \$45,000/QALY - \$75,000/QALY, an increase of 29%. Altering both MFS extrapolation to generalised gamma (from exponential) and OS extrapolation to log-logistic (from Weibull), decreased the ICER to \$45,000/QALY - \$75,000/QALY. Alternatively, changing both the MFS and OS extrapolations to the Gompertz function increased the ICER by 27.8% to \$45,000/QALY - \$75,000/QALY. The ESC noted that due to the immaturity of the trial data the reliability of the parametric extrapolation functions were highly uncertain and that none of the extrapolations provided clinically plausible outcomes. The ESC advised that alternative approaches to modelling such as flexible parametric extrapolations through the use of spline functions to capture the time-dependent effects could be explored. The pre-PBAC Response was uncertain whether the application of spline functions within the short time period of extrapolation would have a significant impact on cost-effectiveness or reduce uncertainty in the model. The PBAC considered that given the uncertainty around the magnitude of survival benefit and immature trial data, a conservative approach to extrapolation may be appropriate.

Drug cost/patient/course

- 6.47 The intervention costs per patient per month or course are shown in Table 14.

³ Wu EQ, Mulani P, Farrell MH, Sleep D. Mapping FACTP and EORTC QLQ-C30 to patient health status measured by EQ-5D in metastatic hormone-refractory prostate cancer patients. *Value Health*. 2007;10(5):408–14.

Table 14: Intervention costs^a per patient across one month and model duration

	Darolutamide		
	Trial dose and duration	Model	Financial estimates
Mean dose	1,186.61 mg/day	1,200 mg/day ^a	1,200 mg/day ^b
Mean duration	16.79 months	2.32 years	NR ^b
Cost/patient/month	-	\$ [REDACTED]	\$ [REDACTED]
Cost/patient/course	-	\$ [REDACTED]	\$ [REDACTED]

Source: ARAMIS CSR_Feb 2019; Excel workbook 'DARO_Section3Model_March2020 FINAL' and DARO_Section4model_March 2020 Supplementary.

^a The economic model applied a dose intensity of 98.88% to darolutamide; cost for one month was assumed to match the cycle cost of 28 days.

^b A dose intensity of 98.88% was applied to darolutamide for the financial estimates and it was assumed [REDACTED] packs would be used in Year 1, [REDACTED] packs in Year 2, [REDACTED] packs in Year 3, [REDACTED] packs in Year 4, [REDACTED] packs in Year 5 and [REDACTED] packs in Year 6.

Estimated PBS usage & financial implications

6.48 The submission was considered by DUSC.

6.49 The submission applied an epidemiological approach to estimate the number of patients eligible for treatment with darolutamide. Table 15 summarises the inputs used for the financial estimates.

Table 15: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Population	Prevalence data: MFS Kaplan Meier data from the SOC arm of ARAMIS was used to estimate a prevalent pool of patients. Incidence data: ACIM, ACD, AIHW and PCBaSe Sweden database.	Estimation of incident and prevalent patients remains uncertain, as acknowledged by the submission.
Uptake rate	Sponsor assumption: [REDACTED]% in Year 1 increasing to [REDACTED]% in Year 6.	Likely to be underestimated in early years of listing given no other agent is currently PBS-listed.
Compliance rate	98.88%	Trial-sourced; considered in sensitivity analyses.
Grandfather patients	N=less than 10,000	Included separately in financial estimates; not included as part of estimation of patient numbers for subsequent therapy. This is likely to have underestimated net cost to the PBS/RPBS.
Dose	600mg twice daily	While dose of darolutamide was consistent with the economic model, the cost of background ADT, which was included in the economic model, was not included in the estimates.
Offsets – subsequent therapy	Cost offsets for subsequent therapy (docetaxel, cabazitaxel only for darolutamide) were estimated.	Agents considered are consistent with the economic model.
MBS items	Not included.	Underestimated the financial implications.

Source: Section 4.1 to Section 4.5, p256-294 of the submission.

ACD=Australian Cancer Database; ACIM=Australian Cancer Incidence and Mortality; ADT=androgen deprivation therapy; AE=adverse event; AIHW=Australian Institute of Health and Welfare; mOCRPC=non-metastatic castration-resistant prostate cancer; mCRPC=metastatic castration-resistant prostate cancer; MFS=metastasis-free survival; SOC=standard of care; TTD=time to treatment discontinuation

6.50 DUSC noted there was no data on the incidence and prevalence of mOCRPC in Australia.

6.51 DUSC considered that the estimates presented in the submission to be uncertain and likely underestimated due to the following:

- The submission stated that prevalence estimates most relevant to the Australian setting suggested that between 8% and 25% of all prostate cancer patients have m0CRPC and between 30% and 40% of these patients are high risk m0CRPC (i.e. have a PSA doubling time ≤ 10 months) (Liede et al. 2013; Saad et al. 2018; Additional sources cited in Section 4 of the submission). DUSC considered these assumptions were uncertain as there was insufficient detail provided in the Liede et al. 2013 publication to verify how the proportion of m0CRPC patients in Australia was derived.
- The assumptions and data informing incidence and prevalence estimates of m0CRPC were highly uncertain and based on published studies from Sweden and Spain. The data in these studies was relatively old and/or small in terms of sample size. It was uncertain how applicable these data were to the proposed PBS population. DUSC commented that the incident and treated patient population was highly uncertain and suggested that the prevalent patient population was likely to be underestimated. The pre-PBAC Response argued that the health care systems and treatments available for CRPC would be comparable between Sweden and Australia given treatment options are largely limited to ADT.
- Darolutamide would be the only available therapy on the PBS for m0CRPC and as such, the uptake rate would probably be higher than estimated in the early years of listing.

6.52 The estimated patient numbers, prescription numbers and costs for the PBS listing of darolutamide are provided in Table 16.

Table 16: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number initiating treatment	■	■	■	■	■	■
Number of scripts ^a	■	■	■	■	■	■
Estimated financial implications of darolutamide						
Cost to PBS/RPBS	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Copayments	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Cost to PBS/RPBS less copayments	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Net financial implications						
Cost to PBS/RPBS	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Cost offsets for change in use of other medicines	-\$ ■	-\$ ■	-\$ ■	-\$ ■	-\$ ■	-\$ ■
Overall net cost to PBS/RPBS	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■

Source: Table 4-22, p284; Table 4-23, p284; Table 4-41, p293 of the submission.

^a Number of scripts based on number initiating treatment, ARAMIS does intensity of 98.88% and expected time to treatment discontinuation sourced from ARAMIS. Patients were assumed to use ■ packs in Year 1, ■ packs in Year 2, ■ packs in Year 3, ■ packs in Year 4, ■ packs in Year 5 and ■ packs in Year 6.

The redacted table shows that at Year 6, the estimated number of scripts dispensed was 10,000 – 50,000.

- 6.53 The total cost to the PBS/RPBS of listing darolutamide was estimated to be \$60 - \$100 million in Year 6, and total more than \$100 million over the first 6 years of listing. DUSC considered that the accuracy of the estimates were limited by the sources used to determine the eligible patient population, the low uptake rate in at least the first 2 years of listing (■■■% in Year 1, ■■■% in Year 2), and the reliance on economic model estimates largely based on the effectiveness of darolutamide observed in the ARAMIS trial to determine cost offsets for mCRPC treatment.
- 6.54 Compliance to darolutamide is based on the ARAMIS trial (98.88%). DUSC considered that compliance was substantially overestimated. DUSC noted that in the real-world setting patients are likely to be older and frailer with less support than received under trial conditions. The pre-PBAC Response noted that a retrospective study by Behl et al. 2017 conducted using the Truven Health MarketScan research databases (October 2012 to December 2014), reported medical possession ratios (defined as the sum of the days of supply of the medication, divided by the number of days between the first fill and the last refill plus the days of supply of the last refill) at 12 months in mCRPC patients administered abiraterone or enzalutamide of 0.95 and 0.92 respectively. Further, the pre-PBAC Response stated that real-world compliance data in the mid-1990s reported in mCRPC patients, for treatments that are known to have more severe adverse event profiles relative to darolutamide, support high rates of compliance in patients receiving darolutamide treatment.
- 6.55 DUSC noted that the submission assumed that less than 10,000 patients receiving therapy in the patient access program would continue to receive PBS-subsidised therapy. DUSC considered the number of, and time on therapy for, grandfathered patients was uncertain as it was not possible to know how far through treatment patients will be if darolutamide becomes PBS listed.
- 6.56 DUSC noted that ADT costs and MBS item costs for doctor visits and PSA testing were not included in the estimates; however, considered that these costs would likely be similar irrespective of whether darolutamide was available on the PBS.

Financial Management – Risk Sharing Arrangements

- 6.57 The submission stated that the sponsor was willing to enter a risk sharing arrangement (RSA) structure with a proposed ■■■% rebate above caps informed by the financial estimates.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of darolutamide for the treatment of patients with mOCRPC who are at high risk of distant metastases. While the PBAC considered that darolutamide provides a substantial benefit for some patients compared with SOC in terms of delaying disease progression, it considered that the magnitude of the OS benefit was modest, and uncertain given the immaturity of the data. The PBAC considered that the modelled survival benefit was likely overestimated, the ICER was high and underestimated, and that a substantial price reduction would be required for darolutamide to be considered suitably cost-effective. Further, the PBAC considered that the estimated financial impact of listing darolutamide on the PBS was uncertain.
- 7.2 The PBAC acknowledged there is a clinical need for effective therapies for patients with mOCRPC who are not adequately controlled with ADT. The PBAC noted that PBS subsidised treatment with enzalutamide and abiraterone is currently available in the metastatic setting only.
- 7.3 The PBAC noted the consumer comments which supported the listing of darolutamide on the PBS for the treatment of mOCRPC.
- 7.4 The PBAC noted there is limited data on the efficacy of abiraterone or enzalutamide following darolutamide, but considered that there is a likelihood of cross-resistance if abiraterone or enzalutamide are used sequentially after darolutamide. Thus, the PBAC advised that the PBS restrictions should prevent the use of abiraterone or enzalutamide following darolutamide, consistent with the current listings for abiraterone and enzalutamide in the metastatic setting.
- 7.5 The PBAC considered that watchful waiting/SOC with ADT was the appropriate comparator, and apalutamide and enzalutamide were appropriate near market comparators.
- 7.6 The PBAC noted that the submission was based on the ARAMIS trial, an on-going randomised, double-blind, multicentre trial comparing darolutamide and placebo (SOC), each in combination with ADT, in patients with mOCRPC at high risk of developing distant metastases. The PBAC noted the trial had a moderate risk of bias due to the potential for unblinding based on known prominent adverse events with nonsteroidal antiandrogen therapies like darolutamide.
- 7.7 At a median follow-up of 17.9 months, treatment with darolutamide resulted in a 59% reduction in the risk metastases or death (MFS HR=0.41; 95% CI: 0.34, 0.50), and the median MFS was 40.4 months for darolutamide compared to 18.4 months for SOC. In the darolutamide arm, 221 (23.1%) patients had a MFS event; however, during the central efficacy imaging review, 50 patients (23% of those with events; 5% of the intention to treat (ITT) population) were retrospectively classified as having metastases at baseline. Similarly in the SOC arm, of the 216 (39.0%) patients with a MFS event, 39 (18% of those with events; 7% of the ITT population) were classified as

- having metastases at baseline. An additional analysis in which patients with documented metastases at baseline were censored at randomisation demonstrated darolutamide reduced the risk of metastases or death by 64% (MFS HR=0.36; 95% CI: 0.29, 0.44).
- 7.8 The PBAC noted that for OS, an updated analysis of the ARAMIS trial with a median follow-up of 29.1 months was presented. The PBAC noted a statistically significant improvement in OS (HR=0.69; 95% CI: 0.53, 0.88) was demonstrated. However, the PBAC considered the magnitude of the OS benefit to be modest with an additional 5.7% of patients in the darolutamide arm alive at 36 months. The PBAC further considered the magnitude of the benefit to be uncertain because of the immaturity of the data with death events in 148 (15.5%) patients in the darolutamide arm and 106 (19.1%) patients in the SOC arm. At the time of the updated analysis, 170/554 (30.7%) patients in the SOC arm had crossed over to receive treatment with darolutamide. The PBAC noted the ITT OS results were used in the economic evaluation which was consistent with the availability of PBS treatments, including abiraterone and enzalutamide, for patients with metastatic disease.
- 7.9 The PBAC noted that darolutamide was associated with a significant delay in the time to a symptomatic skeletal event, initiation of cytotoxic chemotherapy, and pain progression. The PBAC noted that there were no clinically meaningful differences across the darolutamide and SOC arms for any of the quality of life measures.
- 7.10 The PBAC considered that the claim of inferior safety compared with SOC was appropriate. The PBAC noted there was a significantly greater occurrence of rash, fatigue and cardiovascular disorders in the darolutamide treatment arm. The PBAC considered that fatigue/asthenia may have a considerable impact on cognitive function given treatment is likely to be long-term and the majority of the patient population are elderly.
- 7.11 Although noting potential differences across the ARAMIS, SPARTAN and PROSPER trials, the PBAC considered, based on the indirect comparisons of the OS results, that darolutamide was likely non-inferior to apalutamide and enzalutamide. The PBAC considered that darolutamide may be better tolerated compared to apalutamide and enzalutamide due to its reduced penetration of the blood-brain barrier which could potentially result in less central nervous system toxicity.
- 7.12 The PBAC noted that the economic model was similar in structure to the apalutamide model presented at the July 2019 PBAC meeting and incorporated the revisions advised by the PBAC at that time, including use of blinded independent central review MFS, a 10-year time horizon and OS results that had not been adjusted for treatment switching. The PBAC considered that the incorporation of these revisions into the darolutamide model was appropriate.

- 7.13 The PBAC noted that the ICER was sensitive to the methods used to extrapolate MFS and OS and that the majority of the life years and QALYs were gained were in the extrapolated period of the model (i.e. beyond the 4 years of the ARAMIS trial). The PBAC noted that the modelled OS curves did not converge within the 10 year time horizon, and difference in OS at 10 years (■■■■%) was substantially larger than that observed in the ARAMIS trial (5.7% at 3 years). The PBAC further noted that the model predicted ■■■■ of patients treated with darolutamide would be alive at 10 years. The PBAC considered that this was unlikely given the prognosis of patients with mCRPC and the average age at entry to the model was 73.6 years. Overall, the PBAC considered that the OS parametric extrapolations were highly optimistic.
- 7.14 The PBAC noted that the ICER was also sensitive to the utility value for the mCRPC health state, with the value of ■■■■ being substantially lower than the values applied in the m0CRPC health state (■■■■ for darolutamide and ■■■■ for SOC). The PBAC agreed with ESC that the same utility value should be applied to all patients in the m0CRPC health state, and that the value applied for mCRPC was too low given that metastatic disease may initially be asymptomatic. The PBAC considered that ■■■■ was more reflective of end stage palliation.
- 7.15 Overall, the PBAC considered that the base case ICER presented in the submission of \$45,000/QALY - \$75,000/QALY was high and underestimated. The PBAC recalled that in July 2019, it considered that an ICER in the range of \$40,000 to \$45,000 per QALY would be acceptable for apalutamide. The PBAC considered that an ICER in the range of \$40,000 to \$45,000 per QALY would also be required for darolutamide to be considered suitably cost-effective. The PBAC further noted the base case ICER presented in the submission increased substantially with a more clinically appropriate OS extrapolation (Gompertz) and mCRPC utility value (0.635 from Wu et al. 2007) to approximately \$75,000/QALY - \$105,000/QALY.
- 7.16 The PBAC considered the estimated financial impact of more than \$100 million over 6 years to be high and uncertain. The PBAC noted DUSC's concerns regarding the estimated utilisation outlined in paragraph 6.51, and specifically that the number of incident and prevalent patients was highly uncertain given the lack of Australian data. The PBAC considered the uncertainty with the financial estimates could be addressed with a RSA based on revised financial caps and a ■■■■% rebate for expenditure beyond the caps.
- 7.17 The PBAC advised that any future resubmission for darolutamide should be a major submission and include a revised economic model which incorporates more clinically appropriate methods of MFS and OS extrapolation, a more clinically appropriate utility value for the mCRPC health state, and a substantial price reduction to achieve an ICER in the range of \$40,000 to \$45,000 per QALY. The resubmission should also include details of a RSA which appropriately addresses the uncertainty with the financial estimates.

7.18 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

Bayer will continue to work with the PBAC and the Department of Health on the listing of Darolutamide.