

**5.05 Capiwasertib,
Tablet 160 mg,
Tablet 200 mg,
Truqap[®],
AstraZeneca Pty. Ltd.**

1 Purpose of submission

1.1 A Category 1 integrated codependent submission requesting:

- An MBS listing for the testing of AKT-pathway alterations (PI3KCA, AKT1 or PTEN) by Next-Generation Sequencing (NGS) in tumour tissue from patients with locally advanced or metastatic hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) (ie HR+/HER2-) breast cancer following recurrence or progression on or after aromatase inhibitor (AI) therapy, with or without a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor. HER2- was defined as immunohistochemistry [IHC] 0 or 1+, or IHC 2+ and in situ hybridisation [ISH]-.
- A PBS listing for capivasertib (CAPI) in combination with fulvestrant (FULV ie CAPI+FULV) treatment in patients with confirmed AKT-pathway altered (PIK3CA, AKT1 or PTEN) tumour and HR+/HER2- locally advanced or metastatic breast cancer.

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus FULV monotherapy.

1.3 The key PICO components presented in 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	Test: Patient with newly diagnosed locally advanced or progression to metastatic HR+/HER2- breast cancer Drug: Patients with AKT pathway altered (<i>PIK3CA</i> , <i>AKT1</i> or <i>PTEN</i>) tumours will be eligible for CAPI+FULV treatment in 1L or 2L metastatic setting.
Intervention	Test: A test of tumour tissue for the detection of an AKT pathway altered (<i>PIK3CA</i> , <i>AKT1</i> or <i>PTEN</i>) tumour. Drug: CAPI 400 mg (two 200 mg tablets) administered orally twice daily, for 4 days on-treatment followed by 3 days off-treatment in combination with FULV 500 mg (2 x 250mg/5 ml) intramuscular injections at intervals of 1 month. An additional FULV 500 mg dose is to be given 2 weeks after the initial dose.
Comparator	Test: No testing Drug: FULV monotherapy
Outcomes	PFS, OS, PFS2, QoL, and safety
Clinical claim	In patients with AI-resistant HR+/HER2- locally advanced or metastatic breast cancer with a confirmed AKT pathway alteration (<i>PIK3CA</i> , <i>AKT1</i> , or <i>PTEN</i>) tumour, the addition of capivasertib + fulvestrant vs fulvestrant monotherapy led to a statistically significant superior PFS outcome and inferior but manageable safety outcome.

Source: Table 1.1, p9 of the submission

AKT = serine/threonine protein kinase; CAPI = capivasertib; FULV = fulvestrant; HER2- = human epidermal growth factor receptor 2 negative; HR+ = hormone receptor positive; NGS = Next Generation Sequencing; OS = overall survival; PFS = progression-free survival; PFS2 = time from randomisation to second progression or death; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha gene; PTEN = phosphatase and tensin homolog; QoL = quality of life; 1L = first line setting; 2L = second line setting

- 1.4 The submission’s PICO table was not consistent with the agreed PICO confirmation from the PICO Advisory Sub-committee (PASC)¹. The proposed population was potentially broader in terms of the test timing and line of treatment and the submission comparator was limited to FULV, whereas the agreed PICO confirmation identified standard of care as the comparator.

2 Background

Registration status

- 2.1 CAPI was TGA approved on 9 May 2024 for use in combination with FULV for the treatment of adult patients with HR+/HER2- (defined as IHC 0 or 1+, or IHC 2+/ISH-) locally advanced or metastatic breast cancer following recurrence or progression on or after an endocrine based regimen.
- 2.2 The PBAC noted that US Food and Drug Administration (FDA), Canada’s Drug Agency (CDA) and European Medicines Agency (EMA) indications for capivasertib are limited to patients with AKT pathway alterations. In addition, the FDA indication limits treatment to “following progression on at least one endocrine-based regimen in the

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[http://www.msac.gov.au/internet/msac/publishing.nsf/Content/C21E97CBD090988BCA258A6F00832B3E/\\$File/1766%20Ratified%20PICO%20redacted.pdf](http://www.msac.gov.au/internet/msac/publishing.nsf/Content/C21E97CBD090988BCA258A6F00832B3E/$File/1766%20Ratified%20PICO%20redacted.pdf)

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metastatic setting or recurrence on or within 12 months of completing adjuvant therapy”.

- 2.3 The TGA approved dose of CAPI is 400 mg (two 200 mg tablets) taken orally twice daily (BD) approximately 12 hours apart (total daily dose of 800 mg) with or without food, for 4 days followed by 3 days off treatment.

3 Requested listing

- 3.1 Secretariat suggested changes to the proposed restrictions are below, with additions in italics and deletions in strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty (packs)	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
Capivasertib, oral tablet, 200 mg and 160 mg, 64 tablets per pack	1	5	\$10,849.93 (pub) \$ (eff)	TRUQAP® AstraZeneca Pty Ltd
Restriction Summary [new] / Treatment of Concept: [new]				
Category / Program:				
<input checked="" type="checkbox"/> GENERAL - General Schedule (Code GE)				
Prescriber type:				
<input checked="" type="checkbox"/> Medical Practitioners				
Restriction type:				
<input checked="" type="checkbox"/> Authority Required (Telephone/Online PBS Authorities system)				
Administrative Advice:				
<i>Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.</i>				
Administrative Advice: No increase in the maximum quantity or number of units may be authorised				
Administrative Advice: No increase in the maximum number of repeats may be authorised				
Administrative Advice: Special Pricing Arrangements apply				
Episodicity: nil				
Severity: Locally advanced or metastatic				
Condition: Breast cancer				
Indication: Treatment of Locally advanced or metastatic breast cancer				
Clinical criteria:				
The condition must be negative for human epidermal growth factor receptor 2 (HER2) overexpression <i>negative</i>				
AND				
Clinical criteria:				
The condition must be hormone receptor positive,				
AND				
Clinical criteria				
The treatment must be in combination with fulvestrant				
AND				
Clinical criteria:				
The condition must be associated with a Tier I/II variant class 4 or 5 <i>PIK3CA or AKT1 or PTEN gene variants</i>				
AND				
Clinical criteria:				
The treatment must be following recurrence or progression on or after an <i>an</i> endocrine based regimen, with or without a <i>with or without a</i> CDK4/6 inhibitor.				

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AND
Clinical criteria:
The treatment must not be a PBS-subsidised benefit beyond disease recurrence/progression A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.
Treatment criteria
Patient must be undergoing initial treatment with this drug – the following are true: (i) this is the first prescription for this drug, (ii) there has been an absence of disease progression whilst on active treatment with this drug, (iii) this prescription seeks no more than 5 repeat prescriptions; or –
Patient must be undergoing continuing treatment with drug – the following are true: (i) there has been an absence of further disease progression whilst on active treatment with this drug, (ii) this prescription does not seek to re-treat after disease progression, (iii) this prescription seeks no more than 5 repeat prescriptions
Prescribing Instructions:
Retain all pathology imaging and investigative test results in the patient's medical records. Do not submit copies of these as part of the authority application. Confirm that the following information is documented/retained in the patient's medical records once only with the first PBS prescription: 1) Evidence of HER2 gene amplification (evidence obtained in relation to past PBS treatment is acceptable). 2) Evidence of HR status 3) Evidence of a Tier I/II gene variant either: (i) PIK3CA (iii) AKT1 (iv) PTEN (evidence obtained in relation to past PBS treatment is acceptable).

- 3.2 The submission requested a special pricing arrangement (SPA). The effective approved ex-manufacturer's price (AEMP) is \$1 and the published AEMP is \$10,687.80.
- 3.3 Each pack contains 64 tablets, a supply quantity of one pack corresponds to 28 days of treatment at the recommended daily dose. A 160 mg tablet is also available for dose reductions. The price for the 200 mg was the same as the 160 mg tablets. In the economic model, the submission inappropriately assumed a relative dose intensity (RDI) of 86.2% to CAPI costs despite the flat pricing of 200 mg and 160 mg tablets. In addition, dose reductions from 400 mg twice daily (BD) to 320 mg BD, would require a second prescription for the 160 mg tablets, and this presented a risk of wastage. In CAPitello-291 there were approximately 24% (84/355) of patients with one dose reduction of CAPI.
- 3.4 The wording of the requested PBS restriction allows for treatment in patients who have progressed to the advanced or metastatic setting where an endocrine-based regimen was used in an earlier stage of cancer. This implies that treatment with CAPI can be in the first-line (1L) for locally advanced/metastatic breast cancer. The National Comprehensive Cancer Network (NCCN) 2024 guidelines recommend CAPI+FULV in the second-line (2L) setting; and the pivotal trial CAPitello-291 mostly enrolled patients treated in the 2L setting as 76% [539/708] of patients had one prior line of endocrine therapy (ET) for locally advanced or metastatic disease. The Pre-Sub-Committee Response (PSCR) noted that some patients now receive ET plus a CDK4/6 inhibitor in the adjuvant setting to prevent breast cancer recurrence and restricting CAPI+FULV to 2L in the advanced setting may exclude these patients from accessing CAPI+FULV on progression to metastatic/advanced disease.

- 3.5 The ESCs noted that the NCCN (2024) guidelines recommend CAPI+FULV following progression on an ET and a CDK4/6 inhibitor. Although the CAPItello-291 trial and TGA indication allow inclusion of patients with or without prior CDK4/6 inhibitors the ESCs advised that the PBAC may wish to consider limiting treatment to patients with prior CDK4/6 inhibitors consistent with treatment guidelines.
- 3.6 The ESCs noted that the proposed restrictions also allowed treatment beyond the 2L setting. Although this was consistent with inclusion criteria in CAPItello-291 where patients were allowed to have received up to two previous lines of endocrine therapy and one previous line of chemotherapy in the context of advanced disease, less than 25% (176/708) of patients in CAPItello-291 had received previous treatment with 2 or 3 lines of therapy for advanced breast cancer. The PSCR argued that the application CAPI + FULV beyond the 2L setting aligns with the real-world practice of managing metastatic breast cancer, where treatment decisions are highly individualised. The ESCs considered that there were significant applicability issues for the comparator of FULV when considering treatment beyond the 2L setting.
- 3.7 The requested restriction was consistent with the submission’s requested population but was narrower than the TGA indication as it required patients to have “class 4 or 5 PIK3CA or AKT1 or PTEN gene variants”. The Secretariat comments on the restriction noted that “class 4 or 5” should be revised to “tier I/II” consistent with standard terminology for somatic gene variants. However, this was not consistent with the requested MBS item which was limited to characterisation of tier I *PIK3CA*, *AKT1* and *PTEN* gene variants.
- 3.8 The requested restriction was broader than the population in CAPItello-291 as the requested restriction specified that patients must have experienced progression on or after an ET, as opposed to after an aromatase inhibitor (AI) therapy in CAPItello-291. The restriction also did not specify an Eastern Cooperative Oncology Group Performance Status (ECOG PS) requirement as was specified in CAPItello-291 (included only ECOG PS 0-1). The ESCs also noted that the proposed restrictions require patients to be hormone receptor positive, whereas in CAPItello-291 hormone receptor-positive status was defined as estrogen-receptor (ER) expression with or without progesterone-receptor expression. The ESCs considered that the restriction wording should be aligned with the trial population and specify that the condition is ER positive.
- 3.9 The ESCs noted that restrictions for FULV would prevent use of CAPI+FULV for patients previously treated with FULV. CAPItello-291 also excluded patients with prior AKT pathway inhibitors which would include everolimus, however under the proposed restrictions patients treated with everolimus could be treated with CAPI+FULV.
- 3.10 The submission proposed a single treatment phase to include initiating and continuing treatment. However, the requested restriction included administrative advice “Patients may qualify for PBS-subsidised treatment under this restriction once only”. This appears to have been included in error given CAPI is an ongoing therapy.

3.11 The submission stated there would be < 500 grandfathered patients. The submission did not present a separate restriction for grandfathered patients, however a separate restriction was not considered necessary as grandfathered patients would be eligible to continue treatment with CAPI under the proposed restriction.

3.12 The submission’s proposed MBS item descriptor is presented below.

Category 6 – PATHOLOGY SERVICES		
MBS item XXXX		
A test of tumour tissue for full characterisation of tier 1 <i>PIK3CA</i> , <i>AKT1</i> and <i>PTEN</i> gene variants including <i>PTEN</i> copy number variants, associated with abrogation of the AKT pathway, in a patient with:		
<ul style="list-style-type: none"> • locally advanced (inoperable) or metastatic hormone receptor positive, HER2- breast cancer; OR • following recurrence or progression on or after endocrine based regimen, with or without a CDK4/6 inhibitor. 		
As requested by a specialist or consultant physician, to determine eligibility for a treatment listed on the Pharmaceutical Benefits Scheme (PBS) for this context.		
Once per primary tumour diagnosis		
Fee: \$2,200	Benefit: 75% = \$1,650	85% = \$1,870

Source: Table 1.5, p21 of the submission

The commentary noted the submission applied the 85% Medicare rebate and did not consider the Greatest Permissible Gap of \$98.70. The MBS fee after applying the Greatest Permissible Gap was \$2,101.30.

3.13 The MBS item descriptor implied that some patients could be tested in the absence of progression from a prior ET, whereas the requested PBS restriction required that patients must have progressed on an ET. The PSCR argued that the test population should include both patients who progress on adjuvant treatment as well as those in the de novo metastatic setting. The PSCR proposed a revised item descriptor:

"Locally advanced (inoperable) or metastatic hormone receptor-positive, HER2-negative breast cancer; OR early hormone receptor-positive, HER2-negative breast cancer following recurrence or progression on or after an endocrine-based regimen, with or without a CDK4/6 inhibitor"

The ESCs noted that this was not consistent with the PBS restrictions which specify the indication for CAPI+FULV is locally advanced or metastatic breast cancer.

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

4 Population and disease

4.1 In 2023, it was estimated that 20,672 new cases of breast cancer were diagnosed in Australia,² approximately 70% of which were likely to be HR+/HER2-. HR+ breast cancer is characterised by cancer cells that have receptors for oestrogen and/or progesterone.³

² Australian Institute of Health and Welfare, Cancer in Australia 2024. 2024, AIHW: Canberra

³ Howlader, N., et al., US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst, 2014. 106(5)

- 4.2 AKT pathway alterations (*PIK3CA*, *AKT1*, or *PTEN*) are somatic variants that are common in patients with the HR+/HER2- subtype. The submission noted that up to 50% of patients may have an alteration, mainly caused by alterations in *PIK3CA* (~35%) followed by *AKT1* (~10%) and *PTEN* (~5%). This informed the prevalence in the economic model and financial estimates. However, the prevalence of AKT pathway alterations in the literature is variable (CAPItello-291 reported 40.8% [289/708] AKT pathway altered patients and Park 2024 reported ~60% AKT pathway altered patients) and Australian-specific rates are not known.⁴ Pathogenic variations in the *PIK3CA*, *AKT*, or *PTEN* (including *PTEN* loss of function) can lead to hyperactivation of the AKT signalling cascade resulting in proliferation and tumour progression. The AKT node in the signalling pathway has three isoforms (*AKT1*, *AKT2*, and *AKT3*) that are key downstream effectors that mediate cell proliferation and resistance to apoptosis. Alterations may present at the time of cancer recurrence or acquired by means of previous treatment.⁵ The ESCs noted that data from the PALOMA-3 trial (in samples before and after FULV with or without palbociclib) indicated that AKT mutations were relatively stable but 8.2% of *PIK3CA* mutations were acquired following treatment with FULV.⁶
- 4.3 The proposed test for the detection of *PIK3CA*, *AKT1*, or *PTEN* alterations was the Roche AVENIO Comprehensive Genomic Profiling (CGP) assay. Roche AVENIO CGP is an in-house Next Generation Sequencing (NGS) pan-cancer assay that provides comprehensive genomic profiling of solid tumours from formalin-fixed paraffin-embedded (FFPE) tissue samples including *PIK3CA*, *AKT1*, and *PTEN* pathway alterations. It was not clear whether accredited pathology services would adopt the Roche AVENIO CGP as the in-house assay or whether an independently developed in-house assay would be used for AKT pathway testing.
- 4.4 The submission proposed that patients who test positive for an AKT pathway alteration may receive treatment with CAPI+FULV. CAPI is a novel pyrrolopyrimidine-derived compound, and is a potent, selective ATP-competitive inhibitor of all three AKT isoforms (*AKT 1/2/3*). FULV is an oestrogen receptor down-regulator. CAPI+FULV combination therapy concurrently targets the AKT pathway and oestrogen receptor signalling resulting in antiproliferative activity in breast cancer cells; and may restore the cancer cells' sensitivity to ETs.
- 4.5 As noted in paragraph 3.4, the requested PBS restriction would allow for testing and treatment in the 1L advanced or metastatic setting and beyond, as long as the patient

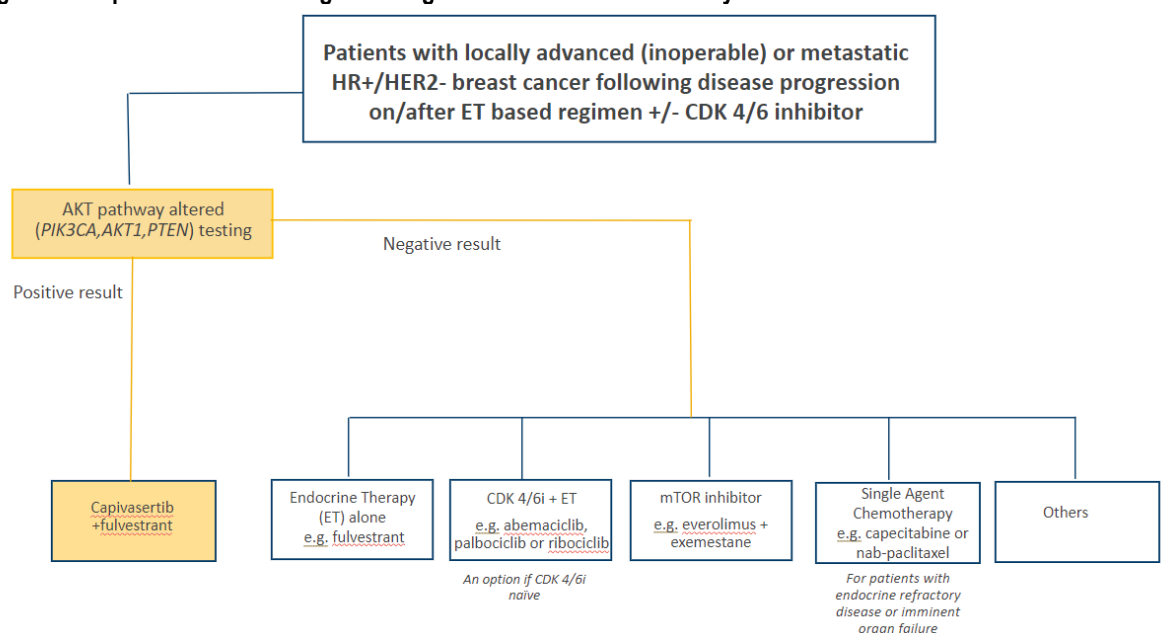
⁴ Park, L, et al., Testing patterns and prevalence of *PIK3CA*, *AKT1*, and *PTEN* alterations among patients (pts) with HR+/HER2- metastatic breast cancer (mBC) in the US. *JCO* 42, 1041-1041(2024). DOI: 10.1200/JCO.2024.42.16_suppl.1041

⁵ Turner, NC, et al. Capivasertib in Hormone Receptor–Positive Advanced Breast Cancer. *N Engl J Med* 2023;388:2058-2070; Vol: 388 No: 22. DOI: 10.1056/NEJMoa2214131

⁶ O'Leary B, et al., The Genetic Landscape and Clonal Evolution of Breast Cancer Resistance to Palbociclib plus Fulvestrant in the PALOMA-3 Trial. *Cancer Discov.* 2018 Nov;8(11):1390-1403. doi: 10.1158/2159-8290.CD-18-0264.

was treated with ET prior to disease progression. The clinical management algorithm present by the submission was reasonable for 2L treatment (see Figure 1) but did not accurately reflect treatment in the 1L or 3L settings (which are allowed under the restriction). Treatment in the 2L setting (following progression on ET and CDK4/6 inhibitor) would be aligned with NCCN 2024 guidelines, and the majority of the patient population in CAPItello-291 trial.

Figure 1: Proposed clinical management algorithm for HR+/HER2- locally advanced or metastatic BC



Source: Figure 1.4, p17 of the submission

AI=aromatase inhibitor; AKT=serine/threonine kinase; BC = breast cancer; CDK 4/6 inhibitor=cyclin dependent kinase 4 and 6 inhibitor; ET=endocrine therapy; ; mTOR=mammalian target of rapamycin; HR+/HER2= hormone receptor–positive/human epidermal growth factor receptor 2; MBS= Medicare Benefits Schedule; *PIK3CA*=phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *mTOR*=mammalian target of rapamycin; *PTEN*=phosphatase and tensin homolog;

Other treatment options may include PIK3 inhibitor (currently none are PBS-listed); poly (ADP-ribose) polymerase (PARP) inhibitors (e.g., olaparib) and trastuzumab deruxtecan (T-DXd).

Note: the proposed algorithm suggested that for patients who test positive to an AKT pathway alteration, the only option available is CAPI+FULV. Instead, the proposed algorithm should indicate that positive patients are still eligible for other 2L therapies

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

5 Comparator

- 5.1 The submission nominated FULV monotherapy as the main comparator for the proposed drug.
- 5.2 The ESCs agreed with the commentary that the submission’s nomination of FULV monotherapy as the only comparator as 2L standard of care (SOC) therapies was not adequately justified. The choice of comparator is complex, and there are subgroups of patients for whom a different therapy could be the appropriate comparator depending on the previous treatments or other biomarkers, as well as the line of treatment for CAPI+FULV. Potential comparators beyond FULV monotherapy are summarised in Table 2. Noting that the requested restriction would allow for

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treatment in the 1L advanced or metastatic setting and beyond, Table 2 also presents the 1L, 2L, and 3L treatment options for HR+/HER2- advanced breast cancer following disease progression with ET with or without CDK4/6 inhibitor.

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Table 2: 1L, 2L, and 3L treatment options for HR+/HER2- advanced breast cancer following disease progression with ET ± CDK4/6 inhibitor

	TGA approved/ PBS-listed	Comment
1L treatment options		
ET+CDK4/6i	Yes/Yes	1L SOC treatment and preferred option for patients who can tolerate treatment. CDK4/6i's are limited to once-per-lifetime use under the PBS, thus only patients who are naïve to CDK4/6i's will be treated (i.e., not treated with a CDK4/6i in early stages of BC).
ET monotherapy	Yes/Yes	Option for patients who may not opt for a CDK4/6i due to issues with tolerability (e.g., older age, frailty).
Chemotherapy	Yes/Yes	Option for patients with imminent organ failure
2L treatment options – no established SOC		
ET+CDK4/6i	Yes/Yes	~30% of pts in CAPItello-291 were naïve to CDK4/6i's at enrolment. Lok 2023 reported 77% of patients from an Australian registry received a 1L CDK4/6i (i.e., ~23% would enter the 2L CDK4/6i-naïve). ⁷ The ESCs considered that patients able to tolerate a CDK4/6i are likely to have been treated in the 1L setting, therefore ET+CDK4/6i is not likely to be a relevant 2L comparator.
ET monotherapy	Yes/Yes	Option for patients who cannot tolerate ET+CDK4/6i therapy and/or do not elect other 2L therapies.
FULV monotherapy	Yes/Yes	The submission elected FULV monotherapy as the main comparator and this was the comparator in CAPItello-291. FULV monotherapy may not be representative of 2L SOC as it is associated with poorer PFS (2-3 months) compared with other treatments. ^{8,9}
EVE+EXE/ tamoxifen/FULV	Yes/Yes	<u>Biomarker = ESR1</u> ESMO 2024 guidelines recommend EVE+EXE/FULV/tamoxifen as 2L therapies.
Olaparib	Yes/No	<u>Biomarker = BRCA1/2</u> Option for patients with concurrent AKT pathway and BRCA alterations. Olaparib was recommended by the PBAC in HR+/HER2- metastatic BC with a confirmed BRCA1/2 mutation in July 2024.
T-DXd	Yes/Yes	Option for patients with HER2-low subtype (a subgroup of the HER2- patient population of this submission). T-DXd is PBS listed for HER2-low unresectable and/or metastatic BC.
Chemotherapy	Yes/Yes	Option for patients with imminent organ failure. The ESCs noted that chemotherapy may also be preferred over FULV for patients without imminent organ failure as PFS benefit is likely to be greater (~7-8 months). ¹⁰
2L Near market comparator		
Alpelisib+FULV	Yes/No	<u>Biomarker = PIK3CA</u> Alpelisib is TGA registered in postmenopausal women and men with HR+/HER2- advanced or metastatic BC with a PIK3CA alteration. Alpelisib has completed the PICO process (1604 Ratified PICO Confirmation). ¹¹
Inavolisib+FULV	No/No	<u>Biomarker = PIK3CA</u> Inavolisib is being investigated in 2L HR+/HER2- locally advanced or metastatic BC with a PIK3CA mutation (NCT05646862). The sponsor for inavolisib also recently lodged an application to MSAC for codependent listing with a PIK3CA test in the 1L advanced setting (MSAC Application 1783). ¹² It is not yet known if CAPI+FULV can be used sequentially after 1L inavolisib.
Pembrolizumab	No/No	<u>Biomarker = PD-L1 CPS ≥1</u> Pembrolizumab is being investigated in an upcoming trial in HR+/HER2- locally recurrent inoperable or metastatic BC with PD-L1 CPS≥1 (NCT04895358, estimated study completion date 21 July 2028). For a subset of patients with PD-L1 CPS≥1, pembrolizumab may be a near market comparator.
3L treatment options		The PASC has noted that subsequent line therapies after disease progression on 2L therapies included alternative therapies that were not used in the 2L.

Source: adapted from Table 3, p16, 1766 Ratified PICO Confirmation, April 2024 PASC Meeting

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AKT=serine/threonine kinase; appr = approved; CAPI = capivasertib; CDK=Cyclin-dependent kinase; CPS = combined positive score; ESMO = European Society for Medical Oncology; ESR1=Estrogen receptor gene 1; ET=endocrine therapy; EVE = everolimus; EXE = exemestane; FULV = fulvestrant; gBRCAm=germline breast cancer gene mutation; HER2 = human epidermal growth receptor 2; PARP=Poly (ADP-ribose) polymerase; PBS=Pharmaceutical Benefits Scheme; PASC = PICO Advisory Sub-Committee; PD-L1 = programmed death ligand-1; PIK3CA=phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN=phosphatase and tensin homolog; SOC = standard of care; T-DXd = trastuzumab deruxtecan; TGA=Therapeutic Goods Administration; 1L = first line setting; 2L = second line setting; 3L= third line setting.

Note:

CDK4/6i includes palbociclib, ribociclib, abemaciclib

ET includes AI (anastrozole, exemestane, letrozole), FULV, tamoxifen,

5.3 In the 1L setting, treatment options include ET monotherapy, ET+CDK4/6 inhibitor, and chemotherapy. ET+CDK4/6 inhibitor is the 1L preferred SOC in those who can tolerate treatment.¹³ While the submission is proposing CAPI+FULV be included as 1L treatment option after ET in the adjuvant setting, in CAPItello-291 only 13% [93/708] of patients were treated in the 1L setting. The PSCR noted that CDK4/6 inhibitors are not relevant comparators in this context as CDK4/6 inhibitors are the treatment of choice in the 1L metastatic setting, therefore it is likely that patients who are proposed to receive CAPI+FULV would have already received a CDK4/6 inhibitor in combination with ET in the adjuvant setting. The ESCs agreed with the PSCR that CDK4/6 inhibitors would be used prior to CAPI+FULV either as adjuvant treatment in the early breast cancer setting or as 1L treatment in the metastatic setting. As such, CDK4/6 inhibitors are not likely to be relevant comparators for CAPI+FULV.

5.4 There are a range of different treatment options in the 2L setting and no clear SOC. Relevant PBS listed therapies include ET monotherapy, mTOR inhibitors in combination with ET (e.g., everolimus + exemestane [EVE+EXE]), or chemotherapy. The PSCR argued that EVE+EXE is not commonly used as it is associated with significant toxicity and has reduced efficacy after CDK4/6 inhibitors and tamoxifen is usually used in earlier lines of treatment.

⁷ Lok, SW, et al., Real world evidence of systemic therapy in hormone receptor positive advanced breast cancer (HR+ ABC) in Australia: ARORA Registry..JCO 41, e13054-e13054(2023). DOI:10.1200/JCO.2023.41.16_suppl.e13054

⁸ Bardia, A., et al. Elacestrant, an Oral Selective Estrogen Receptor Degradar (SERD), Vs Investigator's Choice of Endocrine Monotherapy for ER+/HER2- Advanced/Metastatic Breast Cancer (mBC) Following Progression on Prior Endocrine and CDK4/6 Inhibitor Therapy: Results of EMERALD Phase 3 Trial. In Proceedings of the San Antonio Breast Cancer Symposium, San Antonio, TX, USA, 7–10 December 2021; 2021, p. GS2-02

⁹ Lindeman, G.J., et al. Results from VERONICA: A Randomized, Phase II Study of Second-/Third-Line Venetoclax (VEN) + Fulvestrant (F) Versus F Alone in Estrogen Receptor (ER)-Positive, HER2-Negative, Locally Advanced, Or Metastatic Breast Cancer (LA/MBC). JCO 2021, 39, 1004.

¹⁰ Bardia A, Hu X, Dent R, Yonemori K, Barrios CH, O'Shaughnessy JA, Wildiers H, Pierga JY, Zhang Q, Saura C, Biganzoli L, Sohn J, Im SA, Lévy C, Jacot W, Begbie N, Ke J, Patel G, Curigliano G; DESTINY-Breast06 Trial Investigators. Trastuzumab Deruxtecan after Endocrine Therapy in Metastatic Breast Cancer. N Engl J Med. 2024 Sep 15. doi: 10.1056/NEJMoa2407086. Epub ahead of print. PMID: 39282896.

¹¹ <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1604-public>

¹² <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1783-public>

¹³ Loibl, S. et al. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of Oncology, Volume 35, Issue 2, 159 - 182

- 5.5 The commentary noted that the patient population in the submission (HER2-) included ‘HER2-low’ subtype and trastuzumab deruxtecan (T-DXd) is now PBS listed for the treatment of patients with HER2-low unresectable or metastatic breast cancer. The PSCR stated that T-DXd is reserved for patients who are no longer considered eligible for endocrine treatment. The ESCs noted that the restriction criteria specifies that the “Patient must have received or be ineligible for endocrine therapy in the metastatic setting, if hormone receptor positive”, and therefore the eligible population is consistent with the requested population for CAPI+FULV.
- 5.6 In addition, the commentary noted that the PBAC has recommended olaparib (for patients with BRCA1/2). The PSCR argued that olaparib is specifically indicated for patients with germline BRCA pathogenic variants, whereas CAPI is targeted to patients with AKT pathway alterations, however the ESCs noted that these targets are not mutually exclusive and it is unknown what proportion of patients with AKT pathway alterations would also harbour a germline BRCA pathogenic variant.
- 5.7 While the nominated comparator of FULV monotherapy is a relevant 2L therapy, the ESCs considered that FULV monotherapy was not representative SOC in the 2L+ setting as other viable options may be preferred due to improved efficacy compared with FULV monotherapy¹⁴:
- In patients with BRCA positive tumours olaparib may be used.
 - In patients with HER2 low tumours (a subset of HER2-), trastuzumab deruxtecan may be used.
 - Everolimus+exemestane/FULV/tamoxifen are PBS-listed and are also recommended combination 2L options.
 - Chemotherapy may be preferred in some patients as it is likely to provide longer PFS compared with FULV alone.
 - In addition, at least three potential near market comparators (alpelisib, inavolisib and pembrolizumab) suggest an evolving clinical landscape in which the use of 2L FULV monotherapy may be diminished.
- 5.8 The ESCs agreed with the commentary that it was unlikely that the comparative efficacy between CAPI+FULV with chemotherapy, olaparib or T-DXd as well as near market comparators could be reliably informed with the available evidence and it was unclear if any comparative evidence would be forthcoming in the near future. The ESCs considered that indirect comparisons with these treatments are unlikely to be informative. Nonetheless, the existence of other comparators introduces uncertainty as to the relative benefit and cost effectiveness of CAPI + FULV in clinical practice.

¹⁴ Ashai N, Swain SM. Post-CDK 4/6 Inhibitor Therapy: Current Agents and Novel Targets. *Cancers (Basel)*. 2023 Mar 20;15(6):1855. doi: 10.3390/cancers15061855.

Further, given the options available within and across treatment lines, the comparative treatment effect from CAPItello-291 may have progressively reduced applicability to clinical practice in the near future.

- 5.9 In the 3L setting, the 1766 Ratified PICO Confirmation noted that alternative therapies that were not previously used in the 2L could be used in subsequent lines, and this was supported by NCCN 2024 and The European Society for Medical Oncology (ESMO) 2024 guidelines (1766 Ratified PICO Confirmation, April 2024 PASC Meeting). In CAPItello-291, 21% (76/708) of patients were treated in the 3L setting and 4% (26/708) in the fourth line setting (4L). The ESCs noted that FULV monotherapy is unlikely to be the preferred SOC treatment for patients in the 3L+ setting.

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 3 organisations via the Consumer Comments facility on the PBS website. The input from Rare Cancers Australia described the impact of breast cancer on patients and the challenges of current treatments, including surgery, chemotherapy and hormone therapies. The comments noted the advantage of capivasertib being an oral treatment, potentially allowing patients to return to a more normal daily life while receiving treatment. Input from Breast Cancer Network Australia (BCNA) noted the significant PFS benefit for capivasertib treatment as demonstrated in the CAPItello-291 trial. The comments noted that new therapies provide hope to patients with limited treatment options and noted that patients and their families value any additional months of progression-free or overall survival. Comments from both Rare Cancers Australia and BCNA noted that the high cost of privately funded capivasertib is prohibitive for many patients and PBS subsidy would ensure more equitable access to treatment.
- 6.3 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the capivasertib submission, categorising it as one of the therapies of “high priority for PBS listing” on the basis of the CAPItello-291 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for capivasertib, which was limited to 3 (out of a maximum of 5,

where 5 and 4 represent the grades with substantial improvement), based on a comparison with fulvestrant alone.¹⁵

Overview of the evidence base

- 6.4 The approach taken in the submission was to present evidence that has been linked to support the contention that targeting of AKT pathway alterations (*PIK3CA*, *AKT1*, or *PTEN*) with CAPI+FULV will lead to statistically significantly superior PFS compared to FULV monotherapy in HR+/HER2- locally advanced or metastatic breast cancer patients following disease progression or recurrence on or after an endocrine-based regimen with or without a CDK4/6 inhibitor.
- 6.5 Table 3 presents the summary of evidence informing the linked evidence approach.

¹⁵ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017]

Table 3 Summary of the linked evidence approach

Trial/Study	N	Study design Risk of bias	Population (biomarker)	Intervention/ Test	Comparator/ Clinical utility standard	Key outcomes	Result used in economic model
Diagnostic accuracy (cross sectional) evidence							
Monash Health Pathology 2024	21	CA High	BC (PIK3CA/ AKT1/ PTEN positive only)	Roche AVENIO CGP	F1CDx	PPA, NPA	Not used
FDA 2019	101	CA High	HR+/HER2- BC (PIK3CA)	F1CDx	Externally validated NGS	PPA, NPA	Not used
FDA 2023 *	236	CA Unclear	HR+/HER2- locally advanced or metastatic BC (PIK3CA/ AKT1/ PTEN)	F1CDx	Externally validated NGS	PPV, NPV, PPA, NPA	Not used
Prognostic and predictive validity of the biomarker evidence							
CAPitello-291 ^a	708	P3, R, DB, PC, MC Low ^b	HR+/HER2- LA/M BC after progression or after AI +/- CDK4/6 inhibitor (PIK3CA, AKT1, PTEN)	CAPI + FULV	Placebo + FULV	PFS, OS, HRQoL, DoR, safety	PFS, OS, HRQoL, safety in Altered population
FAKTION ^c	140	P2, R, DB, PC, MC Low (ITT) ^d High (AKT)	Post-menopausal ER+/HER2- LA/M BC after progression or after AI; CDK4/6 inhibitor-naïve (PIK3CA, AKT1, ^e PTEN)	CAPI + FULV	Placebo + FULV	PFS, OS, safety	Not used
SOLAR-1 ^f	572	P3, R, DC, PC, MC Low	Post-menopausal HR+/HER2- LA/M BC before or after progression on ET +/- CDK4/6 inhibitor (PIK3CA)	Alpelisib + FULV	Placebo + FULV	PFS, OS, ORR, safety	Not used
BELLE-3 ^f	432	P3, R, DB, PC, MC Low	Post-menopausal HR+/HER2- LA/M BC before or after progression on or after ET + mTOR inhibitor; CDK4/6 inhibitor-naïve (PIK3CA)	Buparlisib + FULV	Placebo + FULV	PFS, OS, ORR, safety	Not used
Change in clinical management: No evidence was presented for the change in clinical management							

Source: Monash Health Pathology 2024; FDA 2019 report; CAPitello-291, FAKTION, SOLAR-1, BELLE-3; FDA 2023 report
 AKT = serine/threonine protein kinase; AI = aromatase inhibitor; BC = breast cancer; CA = concordance analysis; CAPI = capivasertib; CDK4/6 = cyclin dependent kinase 4 and 6; CGP = comprehensive genomic profiling; DAS = diagnostic accuracy study; DB = double blinded; DoR = duration of response; ET = endocrine therapy; F1CDx = FoundationOneCDx; FDA = Food and Drug Administration; FULV = fulvestrant; HR+ = hormone receptor positive; HER2- = human epidermal growth factor receptor 2 negative; HRQoL = health related quality of life; ITT = intention to treat; LA/M = locally advanced/metastatic; MC = multicentre; mTOR = mammalian target of rapamycin; NGS = next-generation sequencing; NPA = negative percent agreement; ORR = objective response rate; OS = overall survival; PC = placebo controlled; PFS = progression free survival; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha gene; PPA = positive percent agreement; PTEN = phosphatase and tensin homolog; P2 = phase 2; P3 = phase 3; R = randomised

* identified during the evaluation

^a CAPitello-291 informed both the prognostic and predictive validity of AKT pathway alterations.

^b CAPitello-291 was considered low risk of bias overall, but there was potential for reporting bias given the high proportion of patients with unknown AKT status. The non AKT pathway altered subgroups were also exploratory analyses.

^c FAKTION informed both the prognostic and predictive validity of AKT pathway alterations.

^d The ITT cohort in FAKTION was considered low risk, however, the AKT subgroup results were considered to have a high risk of bias given the exploratory *post hoc* nature of these groups

^e AKT1 was not analysed in the original study design. AKT1 testing was conducted at a later date and assessed under the "extended" population

^f SOLAR-1 and BELLE-3 informed the prognostic validity of AKT pathway alterations

Note:

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Risk of bias assessment of diagnostic accuracy studies performing using the QUADAS-2 tool; and for randomised controlled trial using the Cochrane risk of bias tool.

The submission did not present formal evidence to demonstrate the change in management given a positive or negative result for AKT pathway alterations.

- 6.6 The submission presented two concordance analyses to inform the diagnostic accuracy of AKT pathway testing: Monash Health Pathology 2024 and FDA 2019. The FDA 2023 report was identified and included during the evaluation.
- 6.7 Four randomised controlled trials (RCTs) were presented to inform the prognostic effect of AKT pathway alterations based on treatment with placebo + FULV: CAPItello-291, FAKTION, SOLAR-1, and BELLE-3. CAPItello-291 and FAKTION also informed the predictive effect of AKT pathway alterations based on treatment with CAPI+FULV compared to placebo + FULV. An overview of the testing characteristics and mutation cohorts in the prognostic and predictive evidence are presented in Table 4.
- 6.8 The clinical utility standard for the detection of AKT pathway alterations (*PIK3CA*, *AKT1*, or *PTEN*) in the submission is the FoundationOneCDx in tumour tissue samples. FoundationOneCDx is an NGS-based IVD device for the detection of substitutions, insertion and deletion alterations (indels) and copy number alterations in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability, homologous recombination deficiency, and tumour mutational burden using DNA isolated from FFPE tumour tissue specimens. CAPItello-291 and FAKTION (under the 'Expanded' and 'NGS-identified' protocols) used the clinical utility standard and informed the predictive validity of treatment with CAPI+FULV in AKT pathway altered patients. The ESCs noted that there was uncertainty regarding the concordance between Roche AVENIO CGP and FoundationOneCDx and the actual test that will be used in practice was not clear.

Table 4: Overview of testing characteristics and mutation cohorts in the CAPItello-291, FAKTION, SOLAR-1, and BELLE-3

	CAPItello-291	FAKTION	SOLAR-1	BELLE-3
Biomarker tested	<i>PIK3CA</i> , <i>AKT1</i> , and <i>PTEN</i>	Original protocol: <i>PIK3CA</i> and <i>PTEN</i> Updated protocol: <i>PIK3CA</i> , <i>AKT1</i> , and <i>PTEN</i>	<i>PIK3CA</i>	<i>PIK3CA</i>
Assay used	NGS (F1CDx)	Original: ddPCR, IHC, Expanded: ddPCR, NGS (F1CDx GuardantOMNI RUO) NGS: NGS (F1CDx and GuardantOMNI RUO)	PCR (clinical trial assay and theascreen <i>PIK3CA</i> RGQ PCR Kit)	ctDNA (Inostics BEAMing assay), PCR (Roche cobas <i>PIK3CA</i> assay)
Sample	Tissue	Tissue and plasma	Tissue	Tissue or plasma
Positive, n/N (%)	289/708 (41)	Original: 59/140 (42) Expanded: 76/140 (54) NGS: 63/140 (45)	341/572 (60) ^a	ctDNA: 135/348 (39) ^b Tissue: 110/320 (34) ^c
Negative, n/N (%)	313/708 (44)	Original: 81/140 (58) Expanded: 64/140 (46) NGS: 49/140 (35)	231/572 (40) ^a	ctDNA: 213/348 (61) ^b Tissue: 204/320 (64) ^c
Unknown, n/N (%)	106/708 (15)	-	-	Tissue: 7/320 (2)

Source: constructed during the evaluation from Table 2.4, p33; 2.8, p41; Table 2.12, p48; Table 2.13, p51 of the submission; Table 2, Howell 2022 (FAKTION); Table 1, Di Leo 2018 (BELLE-3); Table 1, Andre 2019 (SOLAR-1)

Alp = alpelisib; AKT = serine/threonine kinase; Bup = buparlisib; CAPI = capivasertib; ctDNA = circulating tumour DNA; ddPCR = digital droplet polymerase chain reaction; FULV = fulvestrant; F1CDx = FoundationOneCDx; IHC = immunohistochemistry; ITT = intention to treat; n = number; NGS = Next Generation Sequencing; PBO=placebo; *PIK3CA* = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PTEN* = phosphatase and tensin homolog

^a In SOLAR-1 patients were grouped into *PIK3CA* mutated (N=341) or non-*PIK3CA* mutated cohorts (N=231) and then randomised to receive alpelisib + FULV (*PIK3CA* mutated = 169; non-*PIK3CA* mutated = 115) or placebo + FULV (*PIK3CA* mutated = 172; non-*PIK3CA* mutated = 116)

^b the denominator is the available ctDNA samples collected

^c the denominator is the available tumour tissue samples collected

CAPItello-291: tested for *PIK3CA*, *AKT1*, and *PTEN* using the NGS FoundationOneCDx

FAKTION: tested for *PIK3CA*, *AKT1*, or *PTEN* using three testing protocols: 'Original' AKT pathway altered protocol: digital droplet polymerase chain reaction (ddPCR)/ pyrosequencing and IHC for the detection of *PIK3CA* and loss of *PTEN* expression (tissue and blood samples); 'Expanded' AKT pathway altered protocol: ddPCR/pyrosequencing and NGS (tissue via FoundationOneCDx and blood samples via GuardantOMNI RUO); and 'NGS-identified' AKT pathway altered protocol: NGS (tissue and blood samples)

SOLAR-1: tested for *PIK3CA* alterations using polymerase chain reaction (PCR) of tumour tissue samples (clinical trial assay and theascreen *PIK3CA* RGQ PCR Kit)

BELLE-3: tested for *PIK3CA* alterations was conducted in circulating tumour DNA (ctDNA; Inostics BEAMing assay) and tumour tissue samples (PCR Roche cobas *PIK3CA* assay).

6.9 In CAPItello-291, FAKTION, SOLAR-1, and BELLE-3, the overall risk of bias was low in the intention to treated (ITT) populations. However, there was an unclear to high risk of bias in the AKT altered subgroups since the all analyses in the non AKT pathway altered patients in CAPItello-291, and all AKT pathway subgroups in FAKTION and BELLE-3 were exploratory analyses with some subgroups identified *post hoc*. There also was potential for performance bias in relation to the reporting of subjective outcome measures (e.g., PFS, health related quality of life [HRQoL], safety) in the intervention arms (CAPI+FULV, alpelisib+FULV, buparlisib+FULV) given the higher rates of adverse events (AEs) associated with AKT-inhibitors compared to placebo + FULV may lead to unintentional unblinding of patients.

6.10 CAPItello-291 was most representative of the proposed test setting since CAPItello-291 tested for *PIK3CA*, *AKT1*, and *PTEN* alterations using the clinical utility standard

(FoundationOneCDx) on tumour tissue samples; assessed the comparative effectiveness in patients treated with CAPI+FULV and placebo + FULV; and included patients exposed to CDK4/6 inhibitor therapy (70.1% [496/708]) which may better reflect current clinical practice. However, in CAPItello-291, the AKT pathway altered subgroup being a primary analysis group, the complement subgroup (i.e., the non AKT pathway altered subgroup that included ‘known non AKT pathway altered’ and ‘unknown AKT status’) was treated as exploratory in the trial. As such, there is some uncertainty with the interpretation of results from the complement, in particular when informing the tests for interaction to identify significant treatment effect modifications (Table 9).

- 6.11 There were other potential applicability issues with CAPItello-291 to Australian clinical practice, especially for the 2L setting. Placebo + FULV may not be the relevant comparator for some patients in clinical practice (see paragraph 5.3 and 5.4). Although tests for interaction conducted during the evaluation did not indicate a treatment modification from prior lines of therapy (ET or chemotherapy) or prior CDK4/6 inhibitor use, CAPItello-291 may not have been sufficiently powered to detect such differences. Further, patients previously treated with mTOR inhibitors were excluded from enrolment which was not reflective of the 2L setting in Australia or the requested restriction.
- 6.12 The data available to inform the effectiveness of the AKT pathway testing and treatment with CAPI+FULV included only CAPItello-291 and FAKTION and are presented in Table 5. The AKT pathway alteration subgroups from CAPItello-291 and FAKTION are also presented in Table 6.

Table 5: Data availability to inform comparisons

	CAPI+FULV	FULV monotherapy
Biomarker test positive	CAPItello-291, FAKTION	CAPItello-291, FAKTION
Biomarker test negative	CAPItello-291, FAKTION	CAPItello-291, FAKTION

Source: Section 2A, 2B, 2C, and 2D of the submission
 CAPI = capivasertib; FULV = fulvestrant

Table 6: AKT pathway alteration subgroups informing the predictive effect of AKT pathway testing

AKT pathway subgroups in trials	CAPItello-291
AKT pathway altered	Patients with at least one qualifying <i>PIK3CA</i> , <i>AKT1</i> , or <i>PTEN</i> alteration as detected by NGS F1CDx
Non AKT pathway altered	Patients without a qualifying <i>PIK3CA</i> , <i>AKT1</i> , or <i>PTEN</i> alteration including those who are confirmed Known non AKT pathway altered and unknown AKT status as detected by NGS F1CDx
Known non AKT pathway altered	Patients confirmed to be without a qualifying <i>PIK3CA</i> , <i>AKT1</i> , or <i>PTEN</i> alteration as detected by NGS F1CDx, excluding patients with unknown AKT pathway status
Unknown AKT pathway status	Patients who have an unknown AKT pathway test result due to: <ul style="list-style-type: none"> • Pre-analytical failure (test not performed due to low quality or insufficient sample) • Post-analytical failure (sample was not evaluable) • Test sample not provided
	FAKTION
AKT pathway altered: Original protocol	Patients with at least one qualifying <i>PIK3CA</i> or <i>PTEN</i> alteration as detected by ddPCR or IHC
AKT pathway altered: Expanded protocol	Patients with at least one qualifying <i>PIK3CA</i> , <i>AKT1</i> , or <i>PTEN</i> alteration as detected by ddPCR and NGS (F1CDx and GuardantOMNI RUO)
AKT pathway altered: NGS only protocol	Patients with at least one qualifying <i>PIK3CA</i> , <i>AKT1</i> , or <i>PTEN</i> alteration as detected by NGS only (F1CDx and GuardantOMNI RUO)
Non AKT pathway altered: Original protocol	Patients without a qualifying <i>PIK3CA</i> or <i>PTEN</i> alteration as detected by ddPCR or IHC
Non AKT pathway altered: Expanded protocol	Patients without a qualifying <i>PIK3CA</i> , <i>AKT1</i> , or <i>PTEN</i> alteration as detected by ddPCR and NGS (F1CDx and GuardantOMNI RUO)
Non AKT pathway altered: NGS only protocol	Patients without a qualifying <i>PIK3CA</i> , <i>AKT1</i> , or <i>PTEN</i> alteration as detected by NGS only (F1CDx and GuardantOMNI RUO)

Source: Table 13, p102 CAPItello-291 CSR; p3-4 Howell 2022 FAKTION

AKT = serine/threonine kinase; ddPCR = digital droplet polymerase chain reaction; F1CDx = FoundationOneCDx; IHC = immunohistochemistry; NGS = Next Generation Sequencing; PCR = polymerase chain reaction; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN = phosphatase and tensin homolog

Clinical trials on the safety/effectiveness of CAPI+FULV

- 6.13 The submission was based on one head-to-head trial comparing CAPI+FULV to placebo + FULV: CAPItello-291 (N=708). During the evaluation, FAKTION was included as supplementary evidence since this trial also compared CAPI+FULV to placebo + FULV (N=140), identified AKT pathway alterations using the clinical utility standard (FoundationOneCDx), and had a longer follow-up (median follow-up 58.5 months in the CAPI+FULV arm and 62.3 months in the placebo + FULV arm).
- 6.14 Details of the trials presented in the submission and added during the evaluation are provided in the Table 7.

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Table 7: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
CAPItello-291 NCT04305496 D3615C00001	Clinical Study Report A Phase III Double-blind Randomised Study Assessing the Efficacy and Safety of Capivasertib + fulvestrant Versus Placebo + fulvestrant as Treatment for Locally Advanced or Metastatic Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2 Negative (HR+/HER2-) Breast Cancer Following Recurrence or Progression On or After Treatment with an Aromatase Inhibitor (CAPItello-291) Turner NC, Oliveira M, Howell SJ, Dalenc F, Cortes J, Gomez Moreno HL, Hu X, Jhaveri K, Krivorotko P, Loibl S, Morales Murillo S, Okera M, Park YH, Sohn J, Toi M, Tokunaga E, Yousef S, Zhukova L, de Bruin EC, Grinsted L, Schiavon G, Foxley A, Rugo HS; CAPItello-291 Study Group. Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer.	Version 1, 27 February 2023 N Engl J Med. 2023 Jun 1, Volume: 388, Issue 22, 2058-2070.
FAKTION NCT01992952	Howell SJ, Casbard A, Carucci M, Ingarfield K, Butler R, Morgan S, Meissner M, Bale C, Bezecny P, Moon S, Twelves C, Venkitaraman R, Waters S, de Bruin EC, Schiavon G, Foxley A, Jones RH. Fulvestrant plus capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive, HER2-negative breast cancer (FAKTION): overall survival, updated progression-free survival, and expanded biomarker analysis from a randomised, phase 2 trial. Jones RH, Casbard A, Carucci M, Cox C, Butler R, Alchami F, Madden TA, Bale C, Bezecny P, Joffe J, Moon S, Twelves C, Venkitaraman R, Waters S, Foxley A, Howell SJ. Fulvestrant plus capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive breast cancer (FAKTION): a multicentre, randomised, controlled, phase 2 trial.	Lancet Oncol, 2022 Jul, Volume 23, Issue 7, pp851-864 Lancet Oncol, 2020 Mar, Volume 21, 3, pp345-357

Source: Table 2.37, p97 of the submission

Italicised text indicates studies/trials added during the evaluation

6.15 The key features of the direct randomised trials informing the effectiveness of CAPI+FULV in patients with AKT pathway alterations are summarised in Table 8.

Table 8: Key features of the included evidence

Trials	N	Study design Risk of bias	Population (test; biomarker)	Intervention	Comparator	Key outcomes	Result used in economic model
CAPitello-291 ^a	708	P3, R, DB, PC, MC Low ^b	HR+/HER2- LA/M BC after progression or after AI +/- CDK4/6 inhibitor (F1CDx; <i>PIK3CA</i> , <i>AKT1</i> , <i>PTEN</i>)	CAPI + FULV	Placebo + FULV	PFS, OS, HRQoL, DoR, safety	PFS, OS, HRQoL, safety in Altered population
FAKTION ^c	140	P2, R, DB, PC, MC Low (ITT) ^d High (AKT)	Post-menopausal ER+/HER2- LA/M BC after progression or after AI; CDK4/6 inhibitor-naïve (ddPCR/pyrosequencing, IHC, F1CDx, GuardantOMNI RUO; <i>PIK3CA</i> , <i>AKT1</i> , ^e <i>PTEN</i>)	CAPI + FULV	Placebo + FULV	PFS, OS, safety	Not used

Source: CAPitello-291, FAKTION

AI = aromatase inhibitor; AKT = serine/threonine kinase; BC = breast cancer; CAPI = capivasertib; CDK4/6 = cyclin dependent kinase 4 and 6; DB = double blinded; ddPCR = digital droplet polymerase chain reaction; ER+ = oestrogen receptor positive; ET = endocrine therapy; FULV = fulvestrant; F1CDx = FoundationOneCDx; HR+ = hormone receptor positive; HER2- = human epidermal growth factor receptor 2 negative; HRQoL = health related quality of life; IHC = immunohistochemistry; ITT = intention to treat; LA/M = locally advanced/metastatic; MC = multicentre; OS = overall survival; PC = placebo controlled; PFS = progression free survival; P2 = phase 2; P3 = phase 3; R = randomised

^a CAPitello-291 informed both the prognostic and predictive validity of AKT pathway alterations.

^b CAPitello-291 was considered low risk of bias overall, but there was potential for reporting bias given the high proportion of patients with unknown AKT status. The non AKT pathway altered subgroups were also exploratory analyses.

^c FAKTION informed both the prognostic and predictive validity of AKT pathway alterations.

^d The ITT cohort in FAKTION was considered low risk, however, the AKT subgroup results were considered to have a high risk of bias given the exploratory *post hoc* nature of these groups

^e *AKT1* was not analysed in the original study design. *AKT1* testing was conducted at a later date and assessed under the "extended" population

Comparative effectiveness

- 6.16 In CAPitello-291 at data cutoff (DCO) 1 (15 August 2022) the median follow up was 14.9 months for the CAPI+FULV arm and 14.3 months for the placebo + FULV arm. Only the ITT and AKT pathway altered populations were included in the adjustments for multiplicity; and the non AKT pathway subgroups were exploratory.
- 6.17 In FAKTION, at the DCO (25 November 2021), the median follow up was 58.5 months in the CAPI+FULV arm and 62.3 months in placebo + FULV arm. The AKT pathway subgroups in FAKTION were exploratory and no adjustments for multiplicity were conducted in this trial.
- 6.18 A summary of the PFS results from CAPitello-291 and FAKTION, conditional on AKT pathway alteration status is provided in Table 9. Landmark PFS rates at six, nine and 12 months in CAPitello-291 are presented in Table 12.

Table 9: PFS results for CAPItello-291 and FAKTION in AKT pathway alteration-stratified population treated with either CAPI+FULV or placebo + FULV

Population	CAPI+FULV		PBO + FULV		HR (95% CI); p-value ^{a,b}
	PFS event n/N (%)	Median PFS, months (95%CI)	PFS event n/N (%)	Median PFS, months (95%CI)	
CAPItello-291					
ITT (N=708)	258/355 (72.7)	7.2 (5.5, 7.4)	293/353 (83)	3.6 (2.8, 3.7)	0.60 (0.51, 0.71); <0.001
AKT pathway altered (n=289)	121/155 (78.1)	7.3 (5.5, 9.0)	115/134 (85.8)	3.1 (2, 3.7)	0.50 (0.38, 0.65); <0.001
Non AKT pathway altered (includes unknown) (n=419) ^c	137/200 (68.5)	7.2 (4.5, 7.4)	178/219 (81.3)	3.7 (3, 5)	0.70 (0.56, 0.88); NR
Known non AKT pathway altered (n=313)	103/142 (72.5)	5.3 (3.6, 7.3)	141/171 (82.4)	3.7 (3.5, 5.1)	0.79 (0.61, 1.02); NR
Unknown AKT result (n=106)	34/58 (58.6)	10 (7.3, 11.1)	37/48 (77)	1.9 (1.8, 7.3)	0.52 (0.32, 0.83); NR
Test for interaction^d					
AKT pathway altered vs non AKT pathway altered (Complement)					p=0.0602
AKT pathway altered vs Known non AKT pathway altered (excludes unknown)					p=0.0158^e
FAKTION					
ITT (N=140)	54/69 (78)	10.3 (5, 13.4)	64/71 (90)	4.8 (3.1–7.9)	0.56 (0.38, 0.81); 0.0023
AKT pathway altered					
Original pathway altered (n=59)	26/31 (83)	10.5 (6.6, 18.7)	28/28 (100)	5.2 (3.1, 8.4)	0.47 (0.26, 0.84); 0.011
Expanded pathway altered (n=76)	30/39 (77)	12.8 (6.6, 18.8)	36/37 (97)	4.6 (2.8, 7.9)	0.44 (0.26, 0.72); 0.0014
NGS-identified pathway altered (n=63)	25/34 (74)	13.4 (6.6, 20.7)	29/29 (100)	3.1 (2.8, 7.7)	0.36 (0.20, 0.65); 0.0007
Non AKT pathway altered					
Original pathway non-altered (n=81)	28/38 (74)	10.3 (3.2, 13.5)	36/43 (84)	4.8 (3.0, 10.3)	0.59 (0.35, 0.98); 0.042
Expanded pathway non-altered (n=64)	24/30 (80)	7.7 (3.1, 13.2)	28/34 (82)	4.9 (3.2, 10.5)	0.70 (0.40, 1.25); 0.23
NGS-identified pathway non-altered (n=49)	18/22 (82)	4.8 (1.3, 10.3)	22/27 (81)	5.2 (2.2, 10.5)	0.95 (0.49, 1.82); 0.87
Test for interaction					
'Original' AKT pathway altered vs non AKT pathway altered (Complement) ^f					p=0.18
'Expanded' AKT pathway altered vs non AKT pathway altered (Complement) ^d					p=0.2337
'NGS' AKT pathway altered vs non AKT pathway altered (Complement) ^f					p=0.046^e

Source: adapted from Table 2.31, p82; Table 2.33, p85; Table 2.72, p151 of the submission

CAPI = capivasertib; CI = confidence interval; DCO = data cutoff; HR = hazard ratio; ITT = intention to treat; n = number of participants reporting data; N = total participants in group; NGS = next generation sequencing; NR = not reported; PBO = placebo; PFS = progression free survival

^a 2-sided p-value. Stratified log-rank test. FAKTION was only powered to detect differences in the ITT population and did not adjust for multiplicity.

^b stratified Cox proportional hazards model. A hazard ratio <1 favours capivasertib + fulvestrant. In CAPItello-291, for the Overall Population, the log-rank test and Cox model are stratified by presence of liver metastases (yes vs no), prior use of CDK4/6 inhibitors (yes vs no) and geographic region (Region 1: United States, Canada, Western Europe, Australia and Israel, Region 2: Latin America, Eastern Europe and Russia vs Region 3: Asia). In FAKTION HR was adjusted for pathway status, primary or secondary AI resistance, and measurable and non-measurable disease.

^c the non AKT pathway altered Population comprised of the Known Non AKT pathway altered Population and the Unknown AKT-Result Population

^d Test for interaction conducted during the evaluation

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^e p value < 0.05 suggesting that AKT pathway alteration status was a potentially significant treatment effect modifier

^f Test for interaction was conducted in FAKTION

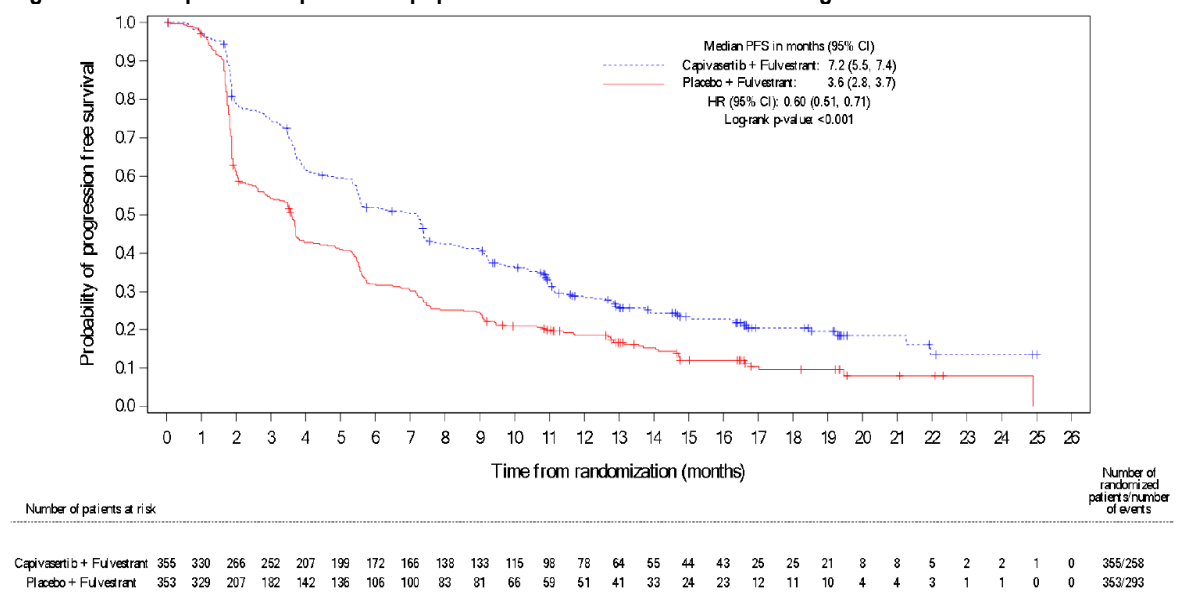
Progression determined by RECIST v1.1.

Bold text indicates a statistically significant result (p<0.05). In FAKTION, the AKT pathway subgroups were not adjusted for multiplicity and therefore are left un-bolded.

Note: In CAPitello-291 at DCO1 15 August 2022 the median follow up was 14.9 months CAPI+FULV arm and 14.3 months PBO+FULV arm. In FAKTION, at DCO 25 November 2021 the median follow up was 58.5 months in CAPI+FULV arm and 62.3 months in PBO+FULV arm

6.19 The PFS Kaplan Meier (KM) plots from CAPitello-291 in the ITT cohort, AKT pathway altered, Known non AKT pathway altered, and unknown AKT status subgroups are shown in Figure 2, Figure 3, Figure 4, and Figure 5, respectively.

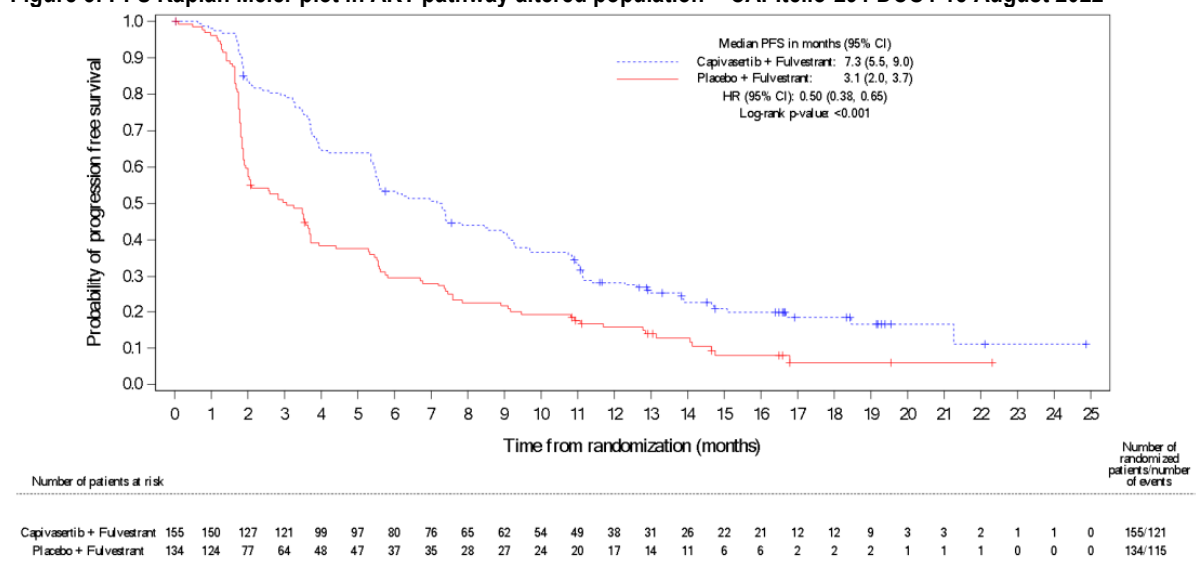
Figure 2: PFS Kaplan Meier plot in ITT population – CAPitello-291 DCO1 15 August 2022



Source: Table 2.53, p128 of the submission

CI = confidence interval; HR = hazard ratio; ITT = intention to treat; PFS = progression free survival

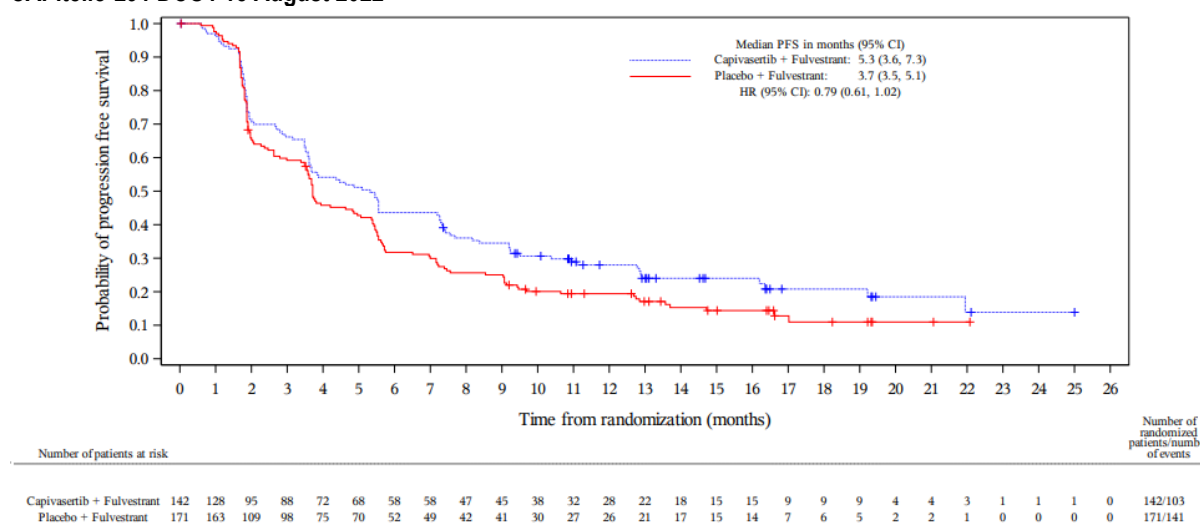
Figure 3: PFS Kaplan Meier plot in AKT pathway altered population – CAPItello-291 DCO1 15 August 2022



Source: Table 2.73, p152 of the submission

CI = confidence interval; HR = hazard ratio; ITT = intention to treat; PFS = progression free survival

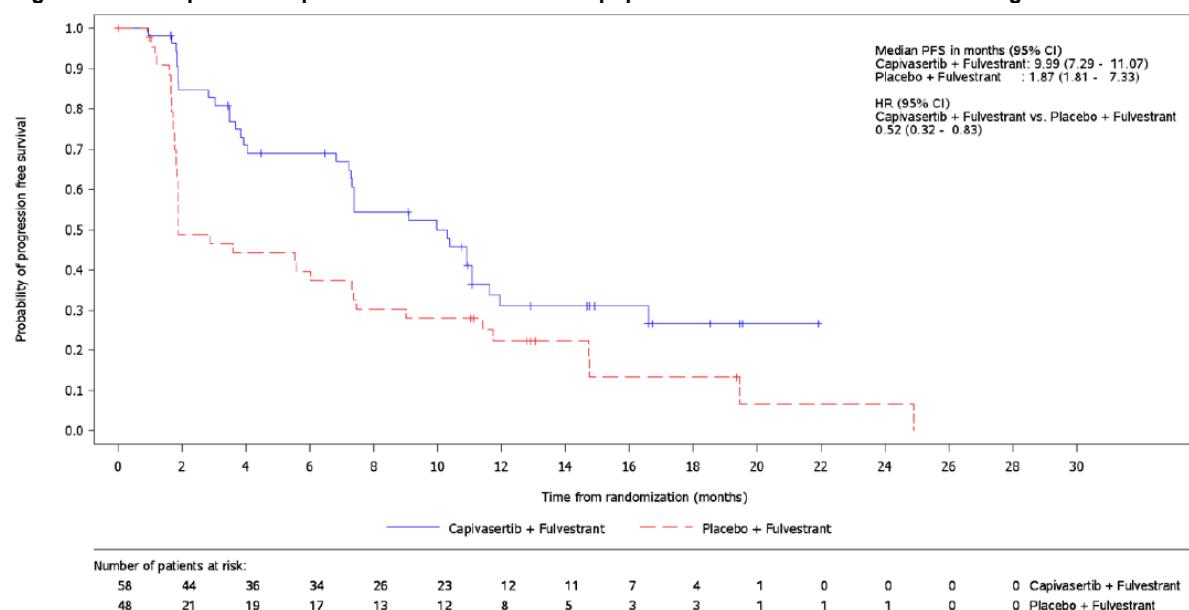
Figure 4: PFS Kaplan Meier plot in Known non AKT pathway altered population (excluding unknown status) – CAPItello-291 DCO1 15 August 2022



Source: Table 2.75, p154 of the submission

CI = confidence interval; HR = hazard ratio; ITT = intention to treat; PFS = progression free survival

Figure 5: PFS Kaplan Meier plot in Unknown AKT status population – CAPitello-291 DCO1 15 August 2022



Source: Table 2.76, p154 of the submission

CI = confidence interval; HR = hazard ratio; ITT = intention to treat; PFS = progression free survival;

- 6.20 CAPitello-291 showed a statistically significant PFS improvement in the CAPI+FULV arm compared to the placebo + FULV arm in the ITT cohort (HR=0.60, 95% CI 0.51, 0.71, p<0.001) and the AKT pathway altered subgroup (HR=0.50, 95% CI: 0.38-0.65, p<0.001). There was also a trend to PFS improvements favouring CAPI+FULV over placebo + FULV in the non AKT pathway (HR=0.70, 95% CI 0.56, 0.88) and unknown AKT status subgroups (HR=0.52, 95% CI 0.32, 0.83). When the unknown results were excluded from the non AKT pathway altered subgroup, the resulting PFS HR in the known non AKT pathway altered subgroup was 0.79 (95% CI 0.61, 1.02) and the 95% confidence interval (CI) included the null. In CAPitello-291, the analyses of known non AKT pathway altered and unknown AKT status subgroups were exploratory analyses conducted post hoc and were not adjusted for multiplicity. As such all analyses in these subgroups should be interpreted with caution.
- 6.21 In FAKTION, there was a trend to a PFS benefit observed in the AKT pathway altered patients identified using the ‘Original’ protocol (PFS HR = 0.47, 95% CI 0.26, 0.84); the ‘Expanded’ protocol (PFS HR = 0.44, 95% CI 0.26, 0.72); and the ‘NGS-identified’ protocol (PFS HR=0.36, 95% CI 0.2, 0.65). In the non AKT pathway subgroups, only the ‘Original’ subgroup showed a PFS benefit (PFS HR = 0.59, 95% CI 0.35, 0.98); the 95% CI around the PFS HR in the ‘Expanded’ (PFS HR=0.7, 95% CI 0.4, 1.25) and ‘NGS-identified’ subgroups (PFS HR=0.95, 95% CI 0.49, 1.82) included the null.
- 6.22 See paragraphs 6.31-6.34 for further discussion on the tests for interaction and predictive value of AKT pathway testing.
- 6.23 A summary of the OS results from CAPitello-291 and FAKTION, conditional on AKT pathway alteration status is provided in Table 10 below.

Table 10: OS results for CAPItello-291 and FAKTION in AKT pathway alteration-stratified population treated with either CAPI+FULV or placebo + FULV

Population	CAPI+FULV		PBO + FULV		HR (95% CI); p-value ^{a, b}
	OS event n/N (%)	Median OS, months (95%CI)	OS event n/N (%)	Median OS, months (95%CI)	
CAPItello-291					
ITT (N=708)	87/355 (24.5)	NE (NE, NE)	108/353 (30.6)	NE (21.7, NE)	0.74 (0.56, 0.98); NE
AKT pathway altered (n=289)	41/155 (26.5)	NE (NE, NE)	46/134 (34.3)	NE (20.3, NE)	0.69 (0.46, 1.05); NE
Non AKT pathway altered (includes unknown) (n=419) ^c	46/200 (23)	NE (NE, NE)	62/219 (28.3)	NE (21.3, NE)	0.76 (0.52, 1.11); NE
Known non AKT pathway altered (n=313)	36/142 (25.4)	NE (22.4, NE)	46/171 (26.9)	NE (21.3, NE)	0.92 (0.59, 1.42); NE
Unknown AKT result (n=106)	NR	NR	NR	NR	NR
FAKTION					
ITT (N=140)	49/69 (71)	29.3 (23.7, 39)	59/71 (83)	23.4 (18.7, 32.7)	0.66 (0.45, 0.97); 0.035
AKT pathway altered					
Original pathway altered (n=59)	20/31 (64)	33.5 (22.3, 50.7)	24/28 (86)	20.9 (15.5, 36.1)	0.50 (0.27, 0.92); 0.025
Expanded pathway altered (n=76)	25/39 (64)	38.9 (23.3, 50.7)	32/37 (86)	20.0 (14.8, 31.4)	0.46 (0.27, 0.79); 0.0047
NGS-identified pathway altered (n=63)	21/34 (61)	39.0 (22.3, 50.7)	25/29 (86)	20.9 (14.1, 35.4)	0.44 (0.24, 0.81); 0.0076
Non AKT pathway altered					
Original pathway non-altered (n=81)	29/38 (76)	26.2 (20.7, 38.5)	35/43 (81)	23.9 (16.3, 33.3)	0.80 (0.49, 1.32); 0.39
Expanded pathway non-altered (n=64)	24/30 (80)	26.0 (18.4, 33.8)	27/34 (79)	25.2 (20.3, 36.2)	0.86 (0.49, 1.52); 0.60
NGS-identified pathway non-altered (n=49)	17/22 (77)	23.7 (16.7, 38.5)	22/27 (81)	25.2 (15.3, 38.8)	0.86 (0.45, 1.63); 0.64

Source: adapted from Table 2.77, pp155-6 of the submission; Figure 14.2.2.15, CAPItello-291 CSR; Table 1, Howell 202

CAPI = capivasertib; CI = confidence interval; HR = hazard ratio; ITT = intention to treat; n = number of participants reporting data; N = total participants in group; NE = not evaluable; NR = not reported; NGS = next generation sequencing; OS = overall survival; PBO = placebo
^a 2-sided p-value. Stratified log-rank test.

^b stratified Cox proportional hazards model. A hazard ratio <1 favours capivasertib + fulvestrant. Stratified by presence of liver metastases (yes vs no), prior use of CDK4/6 inhibitors (yes vs no)

^c the non AKT pathway altered Population comprised of the Known Non AKT pathway altered Population and the Unknown AKT-Result Population

Bold text indicates a statistically significant result (p<0.05). In FAKTION, the AKT pathway subgroups were not adjusted for multiplicity and therefore are left un-bolded.

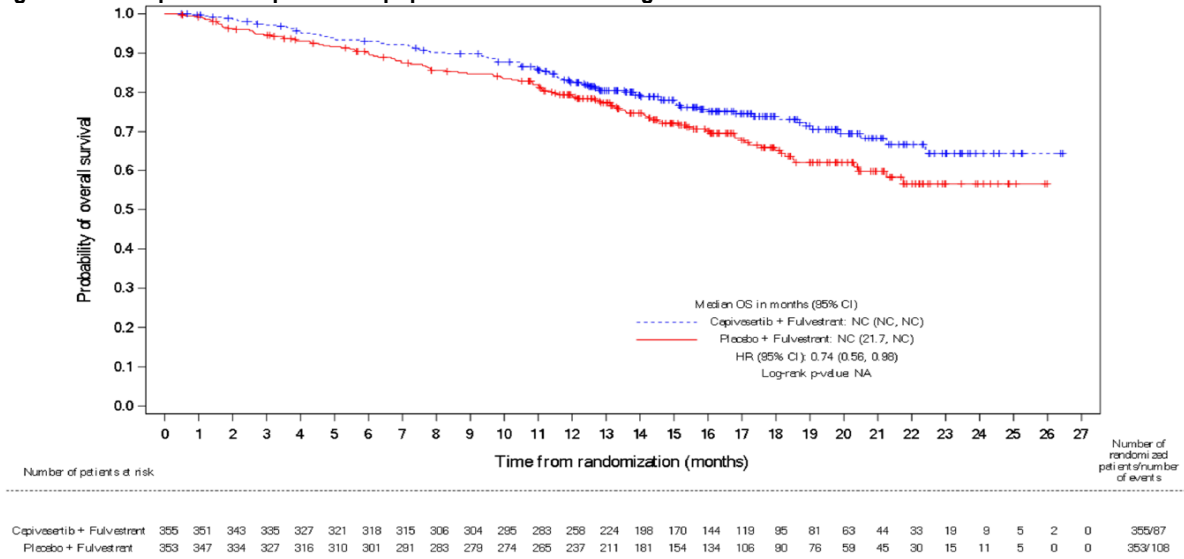
Note:

In CAPItello-291 at DCO1 15 August 2022 the median follow up was 14.9 months CAPI+FULV arm and 14.3 months PBO+FULV arm

In FAKTION, at DCO 25 November 2021 the median follow up was 58.5 months in CAPI+FULV arm and 62.3 months in PBO+FULV arm

6.24 The OS KM plots from CAPItello-291 in the ITT cohort, AKT pathway altered, Known non AKT pathway altered, and unknown AKT status subgroups are shown in Figure 6, Figure 7, Figure 8 and Figure 9, respectively.

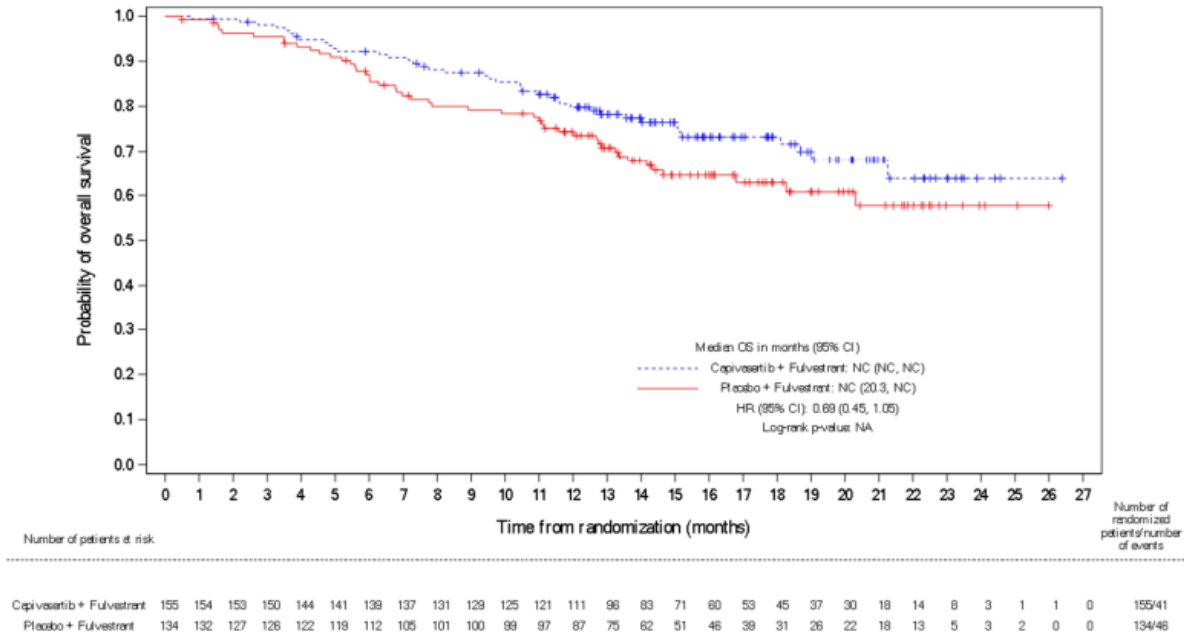
Figure 6: OS Kaplan Meier plot in ITT population - DCO1 15 August 2022



Source: Table 2.55, p130 of the submission

CI = confidence interval; HR = hazard ratio; ITT = intention to treat; OS = overall survival

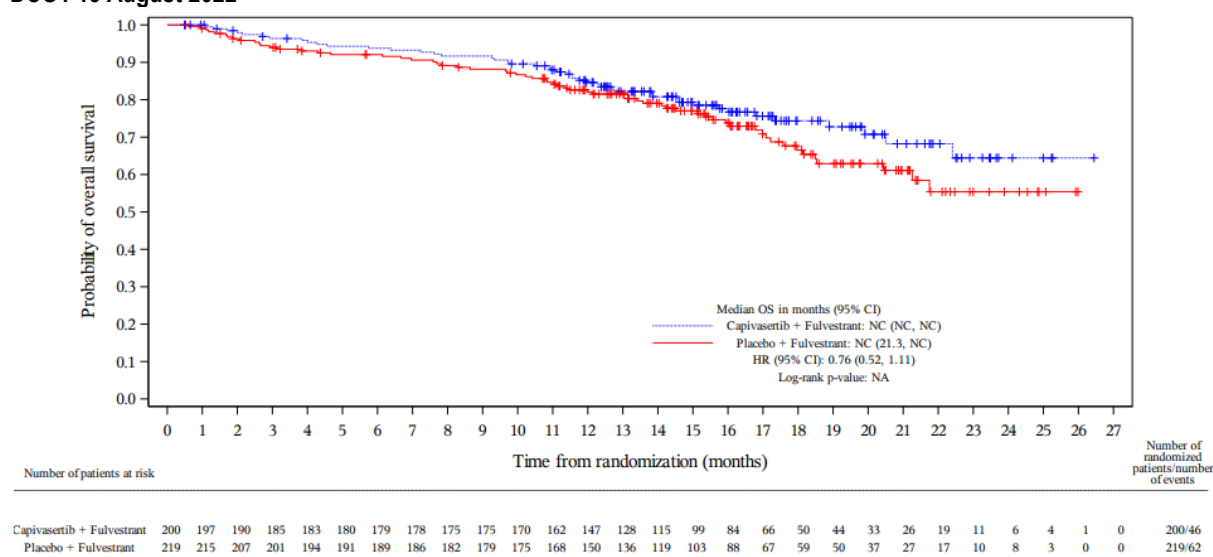
Figure 7: OS Kaplan Meier plot in AKT pathway altered population - DCO1 15 August 2022



Source: Table 2.78, p157 of the submission

CI = confidence interval; HR = hazard ratio; ITT = intention to treat; OS = overall survival

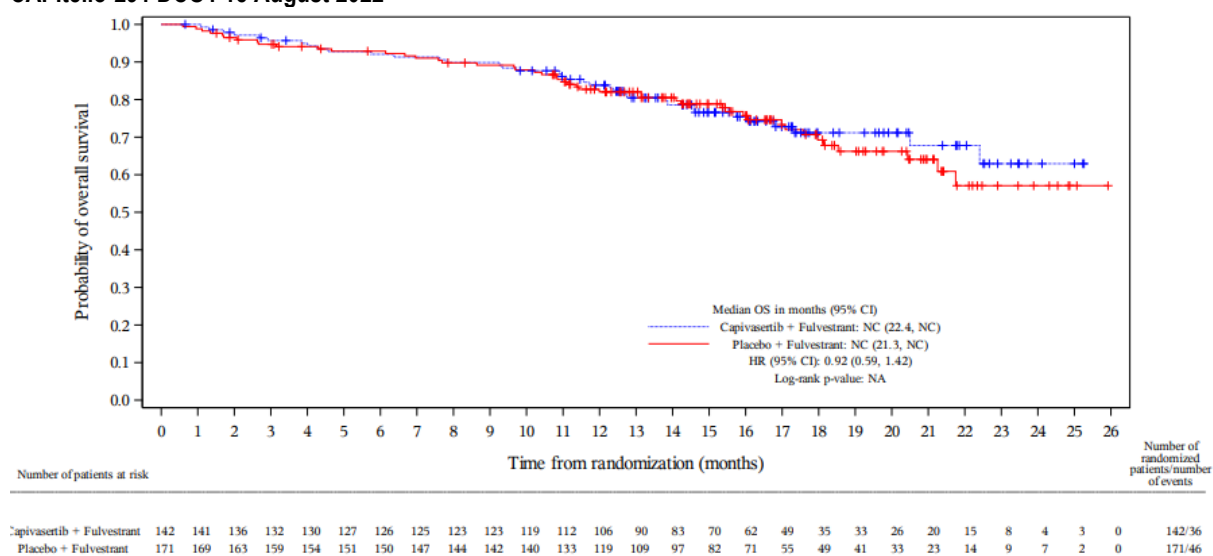
Figure 8: OS Kaplan Meier plot in non AKT pathway altered population (including unknown status) – CAPITello-291 DCO1 15 August 2022



Source: Table 2.79, p157 of the submission

CI = confidence interval; HR = hazard ratio; ITT = intention to treat; OS = overall survival

Figure 9: OS Kaplan Meier plot in Known non AKT pathway altered population (excluding unknown status) – CAPITello-291 DCO1 15 August 2022



Source: Table 14.2.2.15, p28 CAPITello-291 CSR

CI = confidence interval; HR = hazard ratio; ITT = intention to treat; OS = overall survival

6.25 In CAPITello-291, the OS data were immature (only 24.5% [87/355] and 30.6% [108/353] of patients had an OS event at DCO1 in the CAPI+FULV and placebo + FULV arms, respectively). OS was not planned to be formally tested at DCO1. The submission stated that following FDA advice, a bespoke alpha spending function was applied to the assessment of no OS detriment at DCO1, assigning 0.0001 alpha to OS analysis in each of the overall population and the AKT pathway altered population. No statistically significant OS benefit was observed from CAPI+FULV compared to placebo + FULV in the ITT (HR = 0.74, 95% CI 0.56, 0.98) or AKT pathway altered population (HR

- = 0.69, 95% CI 0.46, 1.05) based on the bespoke 0.00001 alpha applied at DCO1. Similar OS HRs were observed for the AKT pathway altered and non AKT pathway altered (including the unknown patients) subgroups, but the 95% CI included the null.
- 6.26 In FAKTION, the ITT population showed an OS HR of 0.66 (95% CI 0.45, 0.97, $p=0.035$) for CAPI+FULV compared to placebo + FULV. OS was a secondary endpoint and no adjustments for multiplicity were performed in FAKTION therefore this result should be interpreted with caution. All three AKT pathway altered subgroups showed an OS HR benefit with a 95% CI that excluded the null ('Original' [OS HR = 0.50, 95% CI 0.27, 0.92]; 'Expanded' [OS HR = 0.46 95% CI, 0.27, 0.79]; and 'NGS-identified' [0.44 95% CI 0.24, 0.81]); whereas all non AKT pathway altered subgroups reported a 95% CI around the OS HR that included the null.
- 6.27 As noted in paragraph 5.8, patients who progressed in CAPItello-291 may have more treatment options available going forward. This may lead to a reduced OS benefit at later data cuts if patients were to be treated with these new therapies, or the applicability of the longer-term OS results may be reduced if patients do not receive these therapies. The PSCR acknowledged that "this dynamic treatment environment makes it challenging for clinical trials to keep pace with the latest advancements and isolate the long-term treatment benefit and effect of capivasertib on OS". The pre-PBAC response noted that the sponsor has received updated OS data from the interim analysis from CAPItello-291 (DCO2) which may be pertinent to the economic decision-making process and may provide further insights into the magnitude of the long-term OS benefits for CAPI+FULV. The sponsor stated that the updated OS data from DCO2 does not impact the PFS gain observed at DCO1 (as maturity for PFS was reached). The PBAC noted that the updated OS data were not provided with the pre-PBAC response and were not available at the time of its consideration.
- 6.28 Progression free survival 2 (PFS2; defined as time to second progression or death in absence of second progression) in the ITT cohort from CAPItello-291 favoured CAPI+FULV arm over the placebo + FULV arm (HR = 0.7, 95% CI 0.57, 0.86); as well as in the AKT pathway altered subgroup (HR = 0.52, 95% CI 0.38, 0.71). The PFS2 results were consistent with the PFS results but were not included in the adjustment for multiple comparisons and interpretation of statistical significance was limited.
- 6.29 The submission also presented duration of response and patient reported health related quality of life (HRQoL) outcomes from CAPItello-291. Median duration of response was similar between treatment arms (9.8 months in CAPI+FULV and 8.4 months in placebo + FULV in the ITT population; 9.4 months in CAPI+FULV and 8.6 months in placebo + FULV in the AKT pathway altered population) though the number of responders was higher in CAPI+FULV (71/355, 20% in CAPI+FULV and 39/353, 11.1% in placebo + FULV in the ITT population; 38/155, 22.6% in CAPI+FULV and 12/134, 8.9% in placebo + FULV in the AKT pathway altered population).
- 6.30 HRQoL was reported using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items (EORTC QLQ- C30), the European

Organisation for Research and Treatment of Cancer Quality of Life Questionnaire breast cancer specific module (EORTC QLQ-BR23) and the Euro-QoL 5-dimension 5-level (EQ-5D-5L) instrument. For EORTC QLQ-C30, there were no clinically meaningful changes (i.e. mean changes were not ≥ 10 points) in global health status/QoL or any of the functional domains except for the role function domain at Cycle 15 for CAPI+FULV and Cycle 19 for placebo + FULV. In the EORTC QLQ-BR23, the risk of clinically meaningful deterioration was comparable between arms for all scales, though the trend was numerically in favour of the CAPI+FULV arm, with all HR <1 . EQ-5D-5L results by progression status were used in the economic model and are discussed in in paragraph 6.75.

Tests for interaction – predictive value of AKT pathway testing

- 6.31 PFS results from CAPItello-291 suggested that AKT pathway altered patients had a greater PFS improvement compared to known non AKT pathway altered patients after treatment with CAPI+FULV (median PFS 7.3 vs 5.3 months). This supported a predictive effect from being AKT pathway altered after treatment with CAPI+FULV. However, the actual complement to the AKT pathway altered subgroup in clinical practice is the subgroup of patients without a positive AKT pathway alteration result (including patients from both known non AKT pathway altered and the unknown AKT pathway status subgroups). The actual complement to the requested population of AKT pathway altered reported a PFS HR that also favoured CAPI + FULV (PFS HR = 0.70, 95% CI 0.56, 0.88).
- 6.32 In CAPItello-291 tests for interaction suggested a significant treatment effect modifier ($p=0.0158$) in the AKT pathway altered and known non AKT pathway altered subgroups (excluding unknown AKT status); but not in the AKT pathway altered subgroup and non-pathway altered (including unknown AKT status) ($p=0.0602$). However, the commentary considered this lack of treatment effect modification may have arisen from the imperfection of the testing procedures of the clinical utility standard (FoundationOneCDx) resulting in a considerable number of unknown results (15% of CAPItello-291) rather than the lack of predictive value of the biomarker.
- 6.33 The results from FAKTION may also suggest that patients who are AKT pathway altered as identified by NGS may have improved PFS benefit from CAPI+FULV compared to placebo + FULV; and there may be no additional benefit from CAPI+FULV in NGS identified non AKT pathway altered patients. Test for interaction in FAKTION suggested a significant treatment effect modifier in the 'NGS-identified' AKT pathway altered subgroup. However, results should be interpreted with caution as the sample sizes informing these subgroups were small; and subgroups were included as exploratory post hoc analyses.
- 6.34 Overall, based on PFS results from CAPItello-291, the commentary concluded that it was likely that CAPI+FULV was more effective than placebo + FULV in AKT pathway altered patients. However, based on available evidence, the efficacy (or lack thereof) in patients without a positive AKT pathway alteration was less clear. The ESCs noted

that the evidence from CAPItello-291 suggested a trend for improved PFS for patients with known non AKT pathway status, however the ESCs considered this may reflect the limitations of testing on archival tissue potentially collected prior to progression on endocrine therapy (see also paragraph 6.48, claim of codependence).

Comparative harms

6.35 A summary of key AEs in CAPItello-291 is presented in Table 11.

Table 11: Summary of key adverse events in the CAPItello-291

AE category	CAPi+ FULV (N=355) ^a	PBO + FULV (N=350) ^a	RD, % (95% CI)	RR (95% CI)
Any AE, n (%)				
Any AE	343 (96.6)	288 (82.3)	14.3 (10.1, 19.0)	1.2 (1.1, 1.2)
Possibly related to CAPi/PBO	318 (89.6)	166 (47.4)	42.1 (35.9, 48.1)	1.9 (1.7, 2.1)
Possibly related to CAPi/PBO only ^b	308 (86.8)	129 (36.9)	49.9 (43.5, 55.8)	2.4 (2.0, 2.7)
Possibly related to both CAPi/PBO and FULV ^b	91 (25.6)	66 (18.9)	6.8 (0.6, 12.9)	1.4 (1.0, 1.8)
Possibly related to FULV only ^b	65 (18.3)	65 (18.6)	-0.3 (-6.0, 5.5)	1.0 (0.7, 1.3)
CTCAE Grade ≥3	152 (42.8)	55 (15.7)	27.1 (20.6, 33.4)	2.7 (2.1, 3.6)
Any SAE, n (%)				
Leading to death	4 (1.1)	1 (0.3)	0.8 (-0.6, 2.6)	3.9 (0.6, 26.2)
Any SAE (including death)	57 (16.1)	28 (8.0)	8.1 (3.3, 12.9)	2.0 (1.3, 3.1)
Any AE leading to discontinuation, n (%)				
Discontinuation of CAPi/PBO	46 (13.0)	8 (2.3)	10.7 (7.0, 14.8)	5.7 (2.8, 11.7)
Discontinuation of CAPi/PBO only	33 (9.3)	2 (0.6)	8.7 (5.9, 12.3)	16.3 (4.4, 61.1)
Discontinuation of both CAPi/ PBO and FULV	13 (3.7)	6 (1.7)	1.9 (-0.5, 4.7)	2.1 (0.9, 5.4)
Discontinuation of FULV only	1 (0.3)	0 (0.0)	0.3 (-0.8, 1.6)	3.0 (0.3, NE)
Any AE leading to dose modification, n (%)^c				
Dose modification of CAPi/PBO	156 (43.9)	43 (12.3)	31.7 (25.4, 37.8)	3.6 (2.7, 4.9)
Dose interruption of CAPi/PBO ^d	138 (38.9)	43 (12.3)	26.6 (20.4, 32.7)	3.2 (2.3, 4.3)
Dose interruption of CAPi/PBO only	124 (34.9)	36 (10.3)	24.6 (18.7, 30.5)	3.4 (2.4, 4.8)
Dose interruption of both CAPi/PBO and FULV	22 (6.2)	9 (2.6)	3.6 (0.6, 6.9)	2.4 (1.1, 5.1)
Dose interruption of FULV only	6 (1.7)	2 (0.6)	1.1 (-0.6, 3.1)	3.0 (0.7, 12.8)
Dose reduction of CAPi/PBO only ^d	70 (19.7)	6 (1.7)	18.0 (13.9, 22.6)	11.5 (5.2, 25.7)
CTCAE Grade ≥3 of interest				
Diarrhoea	33 (9.3)	1 (0.3)	9.0 (6.3, 12.5)	32.8 (5.7, 189.4)
Rash maculo-papular	22 (6.2)	0	6.2 (4.1, 9.2)	44.7 (5.7, NE)
Rash ^b	19 (5.4)	1 (0.3)	5.1 (3.0, 8.0)	18.9 (3.3, 110.7)
Hyperglycaemia	8 (2.3)	1 (0.3)	2.0 (0.4, 4.1)	8.0 (1.3, 48.9)
SAEs of interest				
Diarrhoea	6 (1.7)	1 (0.3)	1.4 (-0.1, 3.4)	6.0 (1.0, 37.6)
Rash maculo-papular	5 (1.4)	0	1.4 (0.3, 3.3)	10.9 (1.3, NE)
Hyperglycaemia	3 (0.8)	0	0.8 (-0.2, 2.5)	7.0 (0.8, NE)

Source: Table 39, p188 CAPItello-291 CSR

AE = adverse event; CAPi = capivasertib; CI = confidence interval; CTCAE = Common Terminology Criteria for Adverse Events; FULV = fulvestrant; NE = not evaluable; PBO = placebo; RD = risk difference; RR = relative risk; SAE = serious adverse event

^a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

^b As assessed by the investigator.

^c For capivasertib/placebo, dose modifications include both dose reductions and dose interruptions. Dose reductions for fulvestrant were not allowed.

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^d The number of dose modifications due to AEs in the exposure summary (capivasertib + fulvestrant arm: 73 patients with dose reductions due to AEs and 137 patients with interruptions due to AEs; placebo + fulvestrant arm: 6 patients with dose reductions due to AEs and 38 patients with interruptions due to AEs; see Section 12.1 CAPItello-291) differs from the number of AEs resulting in a dose modification in this table (capivasertib + fulvestrant arm: 70 patients with AE leading to dose reduction and 138 patients with AEs leading to interruption; placebo + fulvestrant arm: 6 patients with AEs leading to dose reduction and 43 patients with AEs leading to interruption) due to the differences in data capture between the exposure and AE eCRFs.

Adverse events with an onset date on/after date of first dose; AEs with onset date prior to dosing which worsen after dosing; AEs occurring up to 30 days (+ 7 days) following date of last dose are reported.

CTCAE version 5 (23 September 2018), MedDRA version 25.0.

Bold text indicate RD for which 95% confidence interval does not include 0, and RR for which 95% confidence interval does not include 1. *Italicised* text indicates RD and RR analysis performed using StatsDirect during the evaluation comparing CAPI+FULV arm to the PBO + FULV arm. A positive RD indicates higher AE frequency in CAPI+FULV. A RR > 1 indicates that CAPI+FULV was associated with higher rate of AE.

- 6.36 In CAPItello-291, a higher proportion of AEs were reported in patients treated with CAPI+FULV compared to patients treated with placebo + FULV, including serious AEs (SAEs) (16.1% [57/355] vs 8% [28/350]), Grade ≥ 3 AEs (42.8% [152/355] vs 15.7% [55/350]) and AEs leading to discontinuation (13% [46/355] vs 2.3% [8/350]) or dose modifications (43.9% [156/355] vs 12.3% [43/350]). Diarrhoea, rash, and hyperglycaemia were key AEs of special interest. The PBAC noted hyperglycaemia occurred substantially more frequently in patients treated with CAPI than placebo, (17% vs 4%), requiring insulin in 5% of patients treated with CAPI and was persistent in around half of patients who reported hyperglycaemia (28/60 patients). The PBAC also noted that rash occurred substantially more frequently in patients treated with CAPI than placebo (38% vs 7%), with 12% of patients treated with CAPI experiencing a rash of grade 3 or higher. Diarrhoea occurred substantially more frequently in patients treated with CAPI than placebo (72% vs 20%) and was associated with risk of acute kidney injury due to dehydration; 5 (1.4%) patients were reported with acute kidney injury, 2 (0.6%) with renal failure and 4 (1.1%) with renal impairment.
- 6.37 There were four deaths in the CAPI+FULV arm, in which one patient died after experiencing CAPI induced hyperglycaemia. An additional death (due to liver abscess) was reported in the updated safety data from the TGA Delegate Overview, though it was not clear whether this was attributed to CAPI treatment. Generally, the substantial toxicity observed was likely attributed to the addition of CAPI. The safety profile in the overall safety analysis set (SAS) population was similarly observed in the AKT pathway altered SAS population.
- 6.38 The clinical claim of inferior safety of CAPI+FULV was reflected in CAPItello-291. The TGA Delegate Overview had reservations on accepting these toxicities in the context of uncertain clinical benefit. For example, in patients with poorer performance status or diabetes that may increase the risk of hyperglycaemia related toxicities (CAPI TGA Delegate Overview, February 2024). The TGA delegate's overview noted that without clinical evidence, it is not possible to determine the optimal management of CAPI induced hyperglycaemia, however the Advisory Committee on Medicines (ACM) advised that hyperglycaemia is a common side effect of similar therapies used in the field of oncology, and that treating physicians have adequate expertise in managing this condition. The PBAC noted the concerns of the TGA delegate that (i) insulin may not be effective, (ii) there is a potential drug-drug interaction with metformin, and (iii)

use of antidiabetic medications carries a risk of hypoglycaemia on days where capivasertib is not administered. The PBAC noted comments in the TGA delegate overview that the optimal management strategy for management of hyperglycaemia was not clear.

Benefits/harms

6.39 A summary of the comparative benefits and harms for CAPI+FULV versus placebo + FULV is presented in the Table 12.

Table 12: Summary of comparative benefits and harms for CAPI+FULV compared to PBO+FULV

Benefits						
Event	ITT		AKT pathway altered		Absolute Difference	HR (95% CI); p-value
	CAPI+FULV (N=355)	PBO+FULV (N=353)	CAPI+FULV (N=355)	PBO+FULV (N=353)		
Progression free survival (median follow up: 14.9 months CAPI+FULV arm and 14.3 months PBO+FULV arm)						
Progressed, n (%)	258 (72.7)	293 (83)	121 (78.1)	115 (85.8)	-	ITT 0.6 (0.51, 0.71); <0.001
RECIST progression ^a	249 (70.1)	281 (79.6)	115 (74.2)	108 (80.6)	-	
Death in absence of progression ^a	9 (2.5)	12 (3.4)	6 (3.9)	7 (5.2)	-	
Median PFS, months (95% CI)	7.2 (5.5, 7.4)	3.6 (2.8, 3.7)	7.3 (5.5, 9)	3.1 (2, 3.7)	ITT 3.6 m AKT 4.2 m	AKT 0.5 (0.38, 0.65); <0.001
% not progressed at 6 months (95% CI)	51.8 (46.4, 57)	32 (27, 37)	53.4 (45.1, 60.9)	29.6 (21.9, 37.7)	ITT 19.8% AKT 23.8%	
% not progressed at 9 months (95% CI)	40.9 (35.6, 46.1)	24.4 (19.9, 29.1)	42 (34, 49.7)	21.6 (14.9, 29.1)	ITT 16.5% AKT 20.4%	
% not progressed at 12 months (95% CI)	28.5 (23.7, 33.5)	18.4 (14.4, 22.8)	28.2 (21.2, 35.6)	15.8 (10, 22.7)	ITT 10.1% AKT 12.4%	
Harms in the overall population						
	CAPI+FULV (N=355)	PBO+FULV (N=353)	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				CAPI+FULV	PBO+FULV	
Serious AE (including death)	57 (16.1)	28 (8.0)	2.0 (1.3, 3.1)	16	8	8.1 (3.3, 12.9)
Leading to discontinuation	46 (13.0)	8 (2.3)	5.7 (2.8, 11.7)	13	2	10.7 (7.0, 14.8)
Diarrhoea CTCAE Grade ≥3	33 (9.3)	1 (0.3)	32.8 (5.7, 189.4)	9	0	9.0 (6.3, 12.5)
Rash CTCAE Grade ≥3	19 (5.4)	1 (0.3)	18.9 (3.3, 110.7)	5	0	5.1 (3.0, 8.0)
Hyperglycaemia CTCAE Grade ≥3	8 (2.3)	1 (0.3)	8.0 (1.3, 48.9)	2	0	2.0 (0.4, 4.1)

Source: Table 24, p130 of the CAPItello-291 CSR; Table 39, p188 CAPItello-291 CSR

AE = adverse event; CAPI = capivasertib; CI = confidence interval; CTCAE = Common Terminology Criteria for Adverse Events; FULV = fulvestrant; HR = hazard ratio; ITT = intention to treat; n = number of participants reporting data; N = total participants in group; NE = not evaluable; PBO = placebo; PFS = progression free survival; RECIST = Response evaluation criteria in solid tumours; RD = risk difference; RR = relative risk

Bold text indicates a statistically significant p-value

^a percentages expressed as percentage of all patients who experienced a PFS event

6.40 On the basis of direct evidence presented by the submission, for every 100 patients treated with CAPI+FULV in comparison with placebo + FULV over a median duration of follow-up of 14.9 months in the CAPI+FULV arm and 14.3 months in the placebo + FULV arm:

- Approximately 20, 17, and 10 additional patients in the overall population would be progression free at 6-, 9-, and 12-months;

- Approximately 24, 20, and 12 additional patients in the AKT pathway altered population would be progression free at 6-, 9-, and 12-months;
- Approximately 8 additional patients in the overall population would experience a serious AE; 11 additional patients would experience an AE that led to discontinuation of treatment; and
- Approximately 52 additional patients in the overall population would experience a diarrhoea event, 13 additional patients would experience hyperglycaemia (of which 5 patients would require insulin), and 31 additional patients would experience rash.
- Approximately 9 additional patients in the overall population would experience a diarrhoea event of Grade 3 or higher; 5 additional patients would experience a rash event of Grade 3 or higher; 2 additional patients would experience a hyperglycaemia event of Grade 3 or higher.

Clinical claim

- 6.41 The submission described CAPI+FULV as superior in terms of PFS and inferior but with a manageable safety compared to placebo + FULV in patients with HR+/HER2- locally advanced (unresectable) or metastatic breast cancer following progression on or after an ET with or without a CDK4/6 inhibitor, who have an AKT pathway alteration (*PIK3CA*, *AKT1*, or *PTEN*).
- 6.42 The ESCs agreed with the commentary that the claim of superior PFS in AKT pathway altered patients was adequately supported. However, the treatment benefit of CAPI+FULV compared to placebo + FULV in CAPItello-291 may have reduced applicability to Australian clinical practice and any clinical benefit compared to SOC in the Australian setting was potentially overestimated because:
- The comparator, placebo + FULV, may not be representative of 2L SOC available to patients in Australian clinical practice (see paragraph 5.7);
 - Patients in CAPItello-291 were highly heterogeneous and placebo + FULV may not have been the comparator of choice in patients treated in the 1L or 3L+ settings or who were CDK4/6 inhibitor-naïve;
 - Patients previously treated with mTOR inhibitors were excluded from enrolment which was not reflective of the 2L setting in Australia or the requested restriction;
- 6.43 The Evaluation and ESC noted OS data in CAPItello-291 were immature and the OS benefit at later DCOs may be reduced given the evolving treatment landscape in HR+/HER2- advanced breast cancer or have reduced applicability if patients do not receive these newer therapies.
- 6.44 The ESCs agreed with the commentary that the claim of inferior but manageable safety was reasonable. In CAPItello-291 CAPI+FULV was associated with consistently higher rates of AEs compared to placebo + FULV, however, most AEs were managed

with dose interruptions and reductions. Diarrhoea, rash, and hyperglycaemia were most commonly reported after treatment with CAPI, where one death followed CAPI induced Grade 4 hyperglycaemia. There is a potentially higher risk of AEs with CAPI in practice in patients with poorer performance status and/or comorbidities (e.g., hyperglycaemia in diabetic patients).

- 6.45 The PBAC considered that the claim of superior comparative effectiveness was reasonable on the basis of PFS benefit compared to placebo+FULV.
- 6.46 The PBAC considered that the claim of inferior comparative safety to placebo+FULV was reasonable and considered that it was not meaningful to describe the safety of CAPI as “manageable”.

Claim of codependence

- 6.47 The commentary noted that PASC previously considered that AKT pathway testing appeared to predict response in patients treated with CAPI+FULV based on PFS results from CAPItello-291 and FAKTION. CAPItello-291 and FAKTION indicated a greater PFS improvement in AKT pathway altered patients compared to non AKT pathway altered patients, and tests for interaction suggested that AKT pathway alteration was a potential PFS treatment effect modifier. However, the predictive effect of AKT pathway alterations was considered uncertain by the commentary because:
- The PFS benefit remained equivocal in the known non AKT pathway altered and unknown AKT status subgroups as these were conducted *post hoc*, were not adjusted for multiplicity, and characteristics for these subgroups were not presented in the submission.
 - CAPItello-291 and FAKTION did not use the proposed test, Roche AVENIO CGP, to detect AKT pathway alterations and the concordance analysis against FoundationOneCDx was uncertain.
 - Placebo + FULV is not the only 2L SOC and may not be representative of 2L treatments. Therefore, the comparative treatment effect of CAPI+FULV compared to placebo + FULV may not be applicable to inform the predictive significance of AKT pathway alteration status treated with current 2L+ SOC.
- 6.48 The commentary noted that results from CAPItello-291 and tests for interaction conducted during the evaluation suggested AKT pathway alteration was predictive of a PFS benefit when compared to patients with known non AKT pathway alterations (excluding all patients with an unknown AKT alteration test result). This was not observed when compared to all patients who did not have a positive AKT pathway alteration test result. In clinical practice, the complement to the requested population of patients with positive AKT alteration test results would be any patient without a positive AKT alteration test result, which by definition would include all patients with an unknown result. However, the lack of a treatment effect modification in this comparison could be related to the performance of FoundationOneCDx as the clinical utility standard (15% of all patients were classified as having unknown AKT pathway

alteration in CAPItello-291) as opposed to the predictive validity of the biomarker. The ESCs noted that the lack of predictive effect might also reflect the limitations of testing on archival tissue potentially collected prior to progression on endocrine therapy. The ESCs noted that AKT pathway alterations, particularly PIK3CA mutations, could be acquired over time. Therefore, a proportion of patients identified as known non AKT pathway status in CAPItello-291 might have harboured an acquired mutation (i.e. were false negatives). Although the submission noted that fresh tissue samples were preferred for testing, this was not a requirement in the trial or in the proposed item descriptor.

- 6.49 The ESCs considered that testing of fresh tissue (i.e. collected after recurrence or progression on or after endocrine therapy) would be preferable in order to detect any acquired mutations that may be relevant to treatment eligibility. The pre-PBAC response argued that it is standard practice for patients to undergo biopsy sampling at the time of metastatic diagnosis and archival tissue would only be used in a small proportion of patients where biopsy is inappropriate or infeasible. The pre-PBAC also noted evidence from a meta-analysis (Rosin et al 2023) that indicated that there is a low risk of acquired AKT alterations, suggesting that the overall likelihood of missing alterations is minimal.
- 6.50 Overall, the commentary considered it was likely that CAPI+FULV was more effective than placebo + FULV in AKT pathway altered patients. However, the commentary considered there might not be sufficient evidence to support exclusion of patients without a positive AKT alteration test result (i.e., patients without a positive AKT pathway result) from CAPI+FULV treatment. The PSCR argued that “identifying AKT pathway alterations through comprehensive genomic profiling using next generation sequencing (NGS) is pivotal in personalising treatment plans for these patients”. The ESCs agreed with the commentary that there remained some uncertainty regarding the rationale behind excluding patients who did not test positive to AKT pathway alteration from treatment with CAPI+FULV. However, the ESCs advised that consideration should also be given to the fact that CAPI+FULV has inferior safety compared with FULV monotherapy. Given potential safety concerns, treating patients without AKT pathway alterations, who are less likely to benefit from CAPI+FULV, may not be clinically appropriate. The pre-PBAC response argued that “considering the mechanism of CAPI, a therapy targeting the AKT pathway, and the evidence from CAPItello-291 which supports its use in confirmed AKT pathway altered patients, restricting CAPI + FULV to patients with confirmed AKT pathway alterations ensures that those who are treated will derive the highest benefit”.

Economic analysis

- 6.51 The submission presented a modelled economic evaluation, based on the direct randomised trial, CAPItello-291, comparing the proposed test scenario (NGS tumour tissue testing for the detection of AKT pathway alterations [*PIK3CA*, *AKT1*, or *PTEN*]), with the comparator test scenario (no testing) in HR+/HER2- locally advanced or

metastatic breast cancer patients who progressed on or after an ET with or without a CDK4/6 inhibitor.

6.52 Table 13 presents the summary of the economic model components.

Table 13: Summary of model structure, key inputs and rationale

Component	Summary																																	
Comparison modelled	<p>Proposed test scenario: NGS tumour tissue testing for AKT pathway alterations (<i>PIK3CA</i>, <i>AKT1</i>, or <i>PTEN</i>). AKT pathway altered patients are treated with CAPI+FULV, non AKT pathway altered patients and unknown AKT status patients are treated with placebo + FULV</p> <p>Comparator test scenario: No testing. All patients treated with placebo + FULV.</p>																																	
Time horizon	15 years in the model; median follow up was 14.9 months (CAPI+FULV arm) and 14.3 months (PBO+FULV arm) in CAPItello-291																																	
Outcomes	PFS years gained, LYG, QALYs gained																																	
Methods used to generate results	Partitioned survival model																																	
Health states	PF, PD, Death																																	
Cycle length	28-day cycle-length																																	
Test parameters	<p>Based on assumptions: Prevalence = 50% Sensitivity = 99% Specificity = 99% Test failure rate = 5% Test uptake rate = 95%</p>																																	
Implications of false positive and false negative results	<p>False positive patients: treated with and incur costs associated with CAPI+FULV but are assumed to experience PFS and OS of placebo + FULV arm in the ITT cohort from CAPItello-291.</p> <p>False negative and test failure patients: treated with and incur costs associated with placebo + FULV but are assumed to experience PFS and OS of placebo + FULV arm in the ITT cohort from CAPItello-291</p>																																	
Transition probabilities or Allocation to health states (if partitioned survival model)	<p>The allocation of patients to the branches in the proposed and comparator test scenarios were informed by the test parameters. CAPItello-291 was used to inform the PFS and OS curves. The proportions allocated to each branch and data sources informing PFS and OS curves are shown in the table below.</p> <table border="1"> <thead> <tr> <th>Branch</th> <th>% allocation</th> <th>Data source informing PFS and OS</th> </tr> </thead> <tbody> <tr> <td colspan="3">Proposed test scenario</td> </tr> <tr> <td>P1: True positives (Altered)</td> <td>44.7%</td> <td>CAPI+FULV arm from the Altered subgroup</td> </tr> <tr> <td>P2: False negatives (Altered)</td> <td>0.45%</td> <td>PBO+FULV arm from the Altered subgroup</td> </tr> <tr> <td>P3: False positives (non-Altered)</td> <td>0.45%</td> <td>PBO+FULV arm from the ITT cohort</td> </tr> <tr> <td>P4: True negatives (non-Altered)</td> <td>44.7%</td> <td>PBO+FULV arm from the ITT cohort</td> </tr> <tr> <td>P5: Test failure (Altered)</td> <td>4.9%</td> <td>PBO+FULV arm from the ITT cohort</td> </tr> <tr> <td>P6: Test failure (non-Altered)</td> <td>4.9%</td> <td>PBO+FULV arm from the ITT cohort</td> </tr> <tr> <td colspan="3">Comparator test scenario</td> </tr> <tr> <td>C1: Not tested (Altered)</td> <td>50%</td> <td>PBO+FULV arm from the ITT cohort</td> </tr> <tr> <td>C2: Not tested (non-Altered)</td> <td>50%</td> <td>PBO+FULV arm from the ITT cohort</td> </tr> </tbody> </table> <p>Source: constructed during the evaluation from Section 3.2.2 of the submission; Table 3.5, p190 of the submission</p> <p>The model was not sensitive to the changes in the cost and outcomes in branches representing the false negatives (P2), false positives (P3), or test failures (P5 and P6) since these contributed to <5% of the total model cohort.</p>	Branch	% allocation	Data source informing PFS and OS	Proposed test scenario			P1: True positives (Altered)	44.7%	CAPI+FULV arm from the Altered subgroup	P2: False negatives (Altered)	0.45%	PBO+FULV arm from the Altered subgroup	P3: False positives (non-Altered)	0.45%	PBO+FULV arm from the ITT cohort	P4: True negatives (non-Altered)	44.7%	PBO+FULV arm from the ITT cohort	P5: Test failure (Altered)	4.9%	PBO+FULV arm from the ITT cohort	P6: Test failure (non-Altered)	4.9%	PBO+FULV arm from the ITT cohort	Comparator test scenario			C1: Not tested (Altered)	50%	PBO+FULV arm from the ITT cohort	C2: Not tested (non-Altered)	50%	PBO+FULV arm from the ITT cohort
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Public Summary Document – November 2024 PBAC Meeting

Component	Summary																												
Extrapolation method	KM data used until only 20% of patients remained at risk then parametric distributions applied to extrapolate to 15 years. Base case extrapolations are shown in the table below.																												
	<table border="1"> <thead> <tr> <th rowspan="2">Branch</th> <th rowspan="2">Data source</th> <th colspan="3">Parametric distribution</th> </tr> <tr> <th>PFS</th> <th>OS</th> <th>TTD</th> </tr> </thead> <tbody> <tr> <td>-</td> <td>Point of truncation</td> <td>11 months</td> <td>19 months</td> <td>12 months</td> </tr> <tr> <td>P1</td> <td>CAPi+FULV (Altered)</td> <td>Log normal</td> <td>Log normal</td> <td>Log normal</td> </tr> <tr> <td>P2</td> <td>Placebo + FULV (Altered)</td> <td>Log normal</td> <td>Exponential</td> <td>NA</td> </tr> <tr> <td>P3-P6; C1-C2</td> <td>Placebo + FULV (ITT)</td> <td>Log normal</td> <td>Exponential</td> <td>NA</td> </tr> </tbody> </table>	Branch	Data source	Parametric distribution			PFS	OS	TTD	-	Point of truncation	11 months	19 months	12 months	P1	CAPi+FULV (Altered)	Log normal	Log normal	Log normal	P2	Placebo + FULV (Altered)	Log normal	Exponential	NA	P3-P6; C1-C2	Placebo + FULV (ITT)	Log normal	Exponential	NA
	Branch			Data source	Parametric distribution																								
		PFS	OS		TTD																								
	-	Point of truncation	11 months	19 months	12 months																								
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P3-P6; C1-C2	Placebo + FULV (ITT)	Log normal	Exponential	NA																									
Source: Section 3.4.2 and 3.4.3 of the submission																													
In the test scenario (branches P1-P6), 71% of QALYs gained and 34% of total costs occur in the extrapolated period. In the no test scenario (branches C1-C2), 68% of QALYs gained and 39% of total costs occur in the extrapolated period.																													
Health related quality of life	PF = 0.784. Based on EQ-5D-5L data from CAPiello-291 transformed using algorithm by Viney 2011.																												
	PD = 0.623. Based on the average of PD utility values from CAPiello-291 (transformed using Viney 2011) and external sources (Lloyd 2006, previous PBAC considerations including: Olaparib PSD March 2023/November 2023, Olaparib PSD July 2024, Atezolizumab PSD March 2021, Pembrolizumab PSD March 2023, Trastuzumab PSD July 2022, and Sacituzumab govitecan PSD July 2023)																												
	AE disutilities included diarrhoea, rash maculopapular, rash, hyperglycaemia, hypokalaemia. AE rates were from CAPiello-291, and disutility values informed by Nafees 2008, Evans 2023, and Huxley 2017.																												
Healthcare resource use and costs	<p>The submission included the following:</p> <ul style="list-style-type: none"> - Testing costs (proposed fee \$2,200 per test) - CAPI costs (TTD informed by CAPiello-291 and extrapolations) - FULV costs (Treatment duration from CAPiello-291) - Disease monitoring costs (PF and PD health states; clinical expert opinion) - Subsequent anti-cancer therapies (CAPiello-291) - Radiotherapy (clinical expert opinion) - Terminal care costs (informed by Reeve 2018 and T-DXd PSD July 2022) - AE management costs on CAPI or FULV (AE frequency in CAPiello-291) and AE management costs post-progression (AE frequency of chemotherapy in OlympiAD trial) 																												

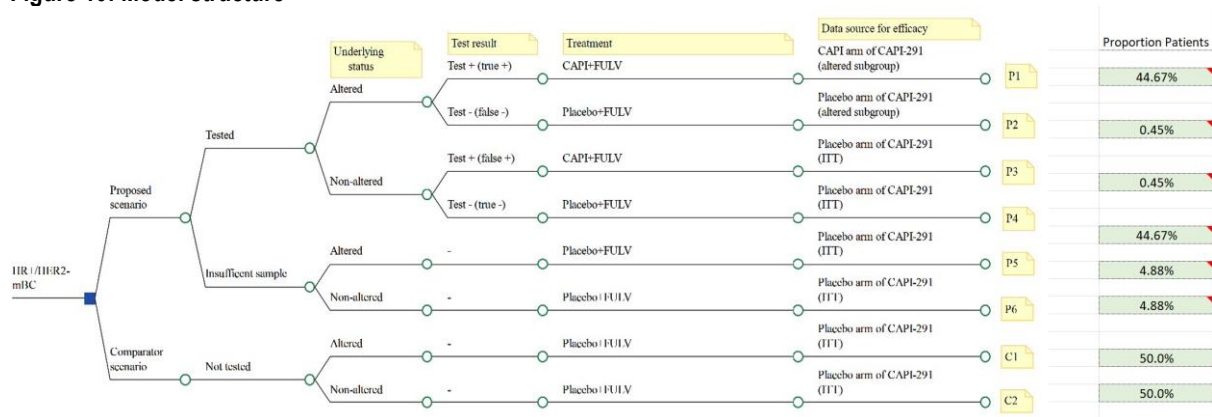
Source: Section 3.2, 3.4, 3.5 of the submission

AE = adverse event; AKT = serine/threonine kinase; CAPI = capivasertib; DCO1 = data cutoff 1; EQ-5D = Euro-QoL 5 dimension; FULV = fulvestrant; ICER = incremental cost effectiveness ratio; ITT = intention to treat; KM = Kaplan Meier; LYG = life year gained; NA = not applicable; OS = overall survival; PBO = placebo; PD = progressed disease; PF = progression free; PFS = progression free survival; PSD = Public Summary Document; PSM = partitioned survival model; QALY = quality adjusted life years; T-DXd = trastuzumab deruxtecan; TTD = time to treatment discontinuation

6.53 The submission assumed that patients eligible for AKT pathway testing enter the model and testing occurs at or soon after diagnosis of HR+/HER2- locally advanced or metastatic disease or at disease progression to metastatic disease setting. Under the proposed test scenario, patients undergo AKT pathway testing and will either receive a test result or the test fails (due to insufficient sample). Positive patients are treated with CAPI+FULV; negative patients are treated with placebo + FULV; and test failure patients are treated with placebo + FULV. Under the comparator scenario, patients do not undergo testing and all patients are treated with placebo + FULV.

6.54 The structure of the economic model is shown in Figure 10.

Figure 10: Model structure



Source: 'Model Outline' worksheet from the economic model

CAPi = capivasertib; FULV = fulvestrant; HR+ = hormone receptor positive; HER2- = Human epidermal growth factor receptor 2 negative; ITT = intention to treat

- 6.55 The comparison between the proposed test scenario and comparator test scenario was appropriate for the claims made in the submission and the request for listing in the AKT pathway altered population. A scenario analysis assuming the non-biomarker selected population were treated with CAPI+FULV was not conducted in the submission. This was performed during the evaluation and led to a 29% increase in the incremental cost effectiveness ratio (ICER) (see paragraphs 6.92 to 6.95).
- 6.56 The data sources informing the test branches were broadly reasonable, however, assuming that non-positive AKT pathway altered patients and patients who do not test would elect treatment with placebo + FULV may not be representative of clinical practice as patients may elect other therapies since FULV monotherapy is not the established SOC in the 1L or 2L+ setting. The incremental benefit for CAPI+FULV is therefore potentially overestimated compared to clinical practice. In addition, informing branches P5 to C2 using the placebo + FULV ITT data instead of data from the respective AKT pathway subgroups added some uncertainty to the ICER (see paragraph 6.60).
- 6.57 The test parameters which informed the proportion of patients within each branch were all based on assumptions that the commentary considered were uncertain and potentially optimistic. In particular, the test failure rate was assumed to be 5% despite 15% of patients in CAPItello-291 having an unknown AKT pathway alteration result. The PSCR stated that in CAPItello-291 69% of unknown samples were due to pre-analytical failure and 13% were due to lack of available sample. The PSCR argued that the rate of pre-analytical failures is expected to be significantly lower in Australian clinical practice as there is more awareness in clinical teams (surgeons/radiologists) around providing adequate, high quality specimens and pathologists are focussed on tissue stewardship to ensure optimal use and preservation. The PSCR also argued that NGS testing is commonly used to determine biomarkers associated with oncology and pathologists believe the failure rate will be 5%. The ESCs considered that it remained

uncertain whether the rate of test failures would be significantly lower in Australian clinical practice than in CAPItello-291 and considered that the use of 5% failure rate was not sufficiently justified.

- 6.58 The diagnostic accuracy evidence of AKT pathway testing was also highly uncertain given the lack of good concordance data and uncertainty about what test will be used in Australian clinical practice. However the model was generally not sensitive to changes to test parameters, with a reduction of sensitivity/specificity from 99% to 90% leading to a 7% increase in the ICER.
- 6.59 The submission assumed a 15-year time horizon in the model. The PBAC has previously accepted a time horizon of 7-10 years in the same population (Ribociclib July 2020, November 2020 and Olaparib July 2024) and also considered a time horizon of 5-years in the same population but at later-line settings (Sacituzumab govitecan July 2023, November 2023). A time horizon of 10 years and 7 years led to a 29% and 75% increase in the ICER, respectively. The PSCR and pre-PBAC response argued that a time horizon of 15 years was reasonable as the mean baseline age of patients in CAPItello-291 was 59 years, PFS is expected to have a sustained treatment benefit, and some sources suggests >10% of patients remain alive at 11 years after diagnosis. The ESCs acknowledged that 15 years of survival may be clinically plausible for some patients, but considered that a shorter time horizon may be more appropriate given the short duration of follow-up for CAPItello-291 (14-15 months) and the high level of uncertainty with regard to longer term outcomes, particularly OS.
- 6.60 The submission modelled the PFS and OS for each branch based on data from three sources from CAPItello-291:
- CAPI+FULV arm in the AKT pathway Altered subgroup (Branch P1; referred to as 'CAPI+FULV (Altered)' herein);
 - Placebo + FULV arm in the AKT pathway Altered subgroup (Branch P2; referred to as 'placebo + FULV (Altered)' herein); and
 - Placebo + FULV arm in the ITT population (referred to as 'placebo + FULV (ITT)' herein) was used in:
 - Branches P3 and P4 (i.e., known non AKT pathway altered). In CAPItello-291, the placebo + FULV (ITT) population showed a slightly lower median PFS compared to the placebo + FULV non AKT pathway altered subgroup (3.6 vs 3.7 months). Applying the slightly lower PFS benefit to the proposed test scenario was a conservative approach.
 - Branches P5 and P6 (i.e., unknown AKT pathway status). In CAPItello-291, the placebo + FULV (ITT) population showed a greater PFS benefit compared to the placebo + FULV arm in the unknown AKT pathway status subgroup (median PFS 3.6 vs 1.9 months). Use of the ITT population for these branches overestimated the benefit in the proposed test scenario.

- Branches C1 and C2 (i.e., comparator branches in the ‘no test scenario’). Using the placebo + FULV (ITT) data instead of the placebo + FULV AKT pathway altered data inflated the benefit in branch C1 (median PFS 3.6 vs 3.1 months, respectively). Whereas using the placebo + FULV (ITT) instead of the placebo + FULV non AKT pathway altered data slightly decreased the benefit in branch C2 (median PFS 3.6 vs 3.7 months, respectively).

It is possible that the impact in branches C1 and C2 was larger than in branches P5 and P6 given a larger patient cohort occupied these branches. However, the net effect on the ICER remains uncertain.

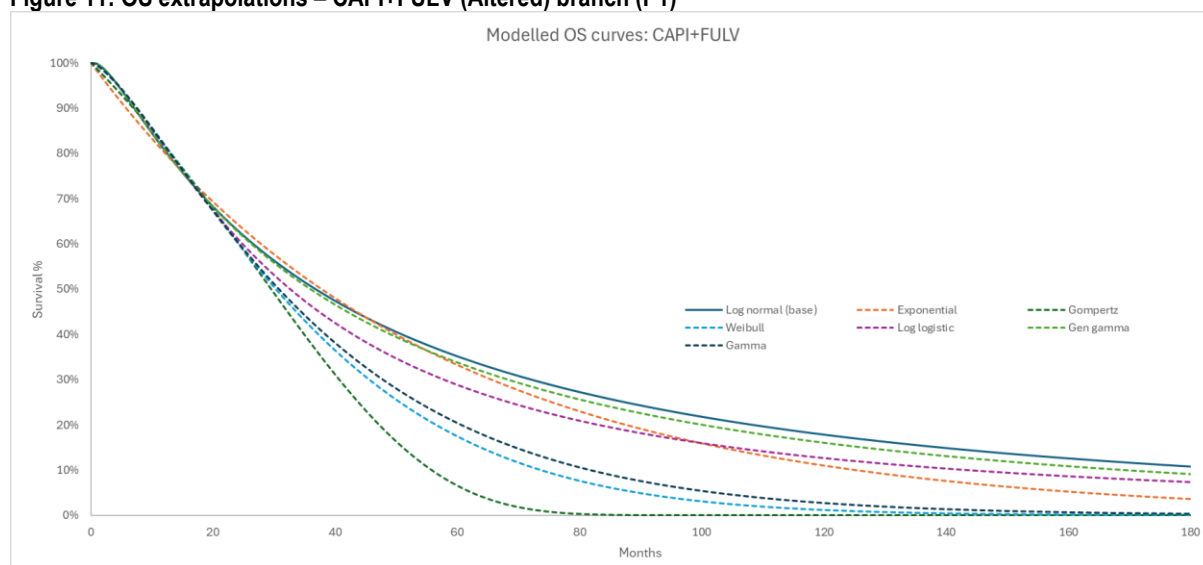
- 6.61 The base case selected the log normal function to model PFS in all branches. The log normal was the best fitting function according to Akaike information criterion (AIC)/Bayesian information criterion (BIC) for the CAPI+FULV (Altered) data and the placebo + FULV (Altered) data (branches P1 and P2); and was the second best fitting function for the placebo + FULV (ITT) branches (P3 to C2; the generalised gamma was the best statistical fit and increased the ICER by 3%). The PFS extrapolations were not a key driver of the model and applying different PFS functions (for all branches) varied the ICER by -12% to +5%.
- 6.62 The base case selected the log normal function to model OS in the CAPI+FULV (Altered) branch (P1), and the exponential function to model OS in the placebo + FULV (Altered) branch (P2) and the placebo + FULV (ITT) branches (P3 to C2). Assessment of proportional hazards (PH) provided in an attachment to the submission did not strongly suggest the PH was upheld, and it might have been reasonable to model PFS and OS with independent functions. Nonetheless, sensitivity analyses testing the same functions for PFS or OS were conducted during the evaluation (Table 21). No convergence to OS was applied, despite extrapolating from around 15 months of follow-up in CAPItello-291 to 15 years in the model. This introduced substantial uncertainty in the economic evaluation. Applying the log normal or log logistic function to OS for all branches implicitly modelled convergence and substantially increased the ICER (+215% and +221%, respectively).
- 6.63 The submission presented a validation of the modelled OS in the CAPI+FULV (Altered) branch against the OS in the CAPI+FULV arm of FAKTION (‘Expanded’ AKT pathway subgroup) and OS estimates from a study by Grinda 2021. Grinda 2021 was a retrospective observational cohort study of 20,446 metastatic breast cancer patients (n=13,590 HR+/HER2- subtype) who initiated treatment in 18 French Cancer Centres between January 2008 and December 2017.¹⁶ The median follow-up was 65.5 months. During the evaluation the ‘NGS-identified’ AKT pathway subgroup from FAKTION and

¹⁶ Grinda, T, et al. Evolution of overall survival and receipt of new therapies by subtype among 20 446 metastatic breast cancer patients in the 2008-2017 ESME cohort. ESMO Open, Volume 6, Issue 3, 100114

the alpelisib+FULV arm from SOLAR-1 in PIK3CA-altered patients were also added to the validation.

6.64 The OS extrapolations for the CAPI+FULV (Altered) branch are presented in Figure 11 and the AIC, BIC and landmark OS estimates from the extrapolations compared to the published trials/studies are presented in Table 14. AIC and BIC values were generally similar across functions, however there was substantial variation in OS estimates between functions. For example, at 5-years the lowest modelled OS estimate in the CAPI+FULV (Altered) branch was 3.6% (Gompertz) and the highest was 33.8% (generalised gamma; and was 32.6% for the log normal i.e., base case).

Figure 11: OS extrapolations – CAPI+FULV (Altered) branch (P1)



Source: constructed during the evaluation from 'Extrapolations CAPI (P1)' worksheet from the economic model
CAPI = capivasertib; FULV = fulvestrant; OS = overall survival

Table 14: Comparison of modelled OS for CAPI+FULV (Altered) branch with the published trials/studies

Landmark OS	CAPI + FULV (Altered) in economic evaluation							Published trials/studies			
	Weibull	Gamma	Gompertz	Gen gamma	Log logistic	Exp	Log normal (base case)	FAKTION (CDK4/6i naïve) ^{a,b}		SOLAR-1 PIK3CA altered ^{b,c}	Grinda 2021 (n=13590)
								'Expanded' AKT Altered	'NGS-identified' AKT Altered		
AIC	409.9	409.5	412.3	410.5	409.2	411.9	408.5	-	-	-	-
BIC	416.0	415.6	418.4	419.6	415.3	414.9	414.6	-	-	-	-
1 years	78.3%	78.3%	78.3%	80.9%	81.5%	78.3%	78.3%	89%	~89%	~88%	~85%
2 years	57.5%	57.9%	56.9%	62.7%	61.2%	61.5%	60.9%	66%	~66%	~69%	~70%
3 years	38.0%	39.6%	32.8%	49.9%	46.3%	48.2%	48.2%	50%	~52%	~55%	~56%
4 years	23.8%	26.4%	13.9%	38.0%	33.5%	37.8%	39.2%	-	-	~35%	-
5 years	14.3%	17.3%	3.6%	33.8%	28.8%	29.7%	32.6%	~23%	~28%	-	35.7%
10 years	0.7%	1.9%	0.2%	16.0%	12.7%	8.7%	15.7%	-	-	-	~12%
15 years	0.0%	0.2%	0.0%	9.1%	7.4%	2.5%	8.9%	-	-	-	-
Median OS	28.2 months	28.8 months	27 months	36 months	33 months	34 months	33.6 months	38.9 months	39 months	39.3 months	42.9 months

Source: constructed during the evaluation from 'Extrapolations CAPI (P1)' worksheet from the economic model; Figure 4D, p861 FAKTION; Supplemental Figure 2D FAKTION; Figure 1, p210 SOLAR-1 updated OS and Table 3.10, p203 of the submission

AIC = Akaike information criterion; BIC = Bayesian information criterion; ;AKT = serine/threonine kinase; CDK4/6i = cyclin dependent kinase 4 and 6 inhibitor; ET = endocrine therapy; Exp = exponential function; ITT = intention to treat; OS = overall survival; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

^a CAPI+FULV arm from the AKT pathway altered subgroups ('Expanded' and 'NGS-identified subgroups) from FAKTION

^b OS estimates from FAKTION and SOLAR-1 were based on visual inspection of Kaplan Meier curves

^c OS estimates were from the alpelisib+FULV arm of SOLAR-1

Italicised text indicates information add during the evaluation (gen gamma and log logistic values and KM data from FAKTION and SOLAR-1 and Grinda 2021 and 4-year modelled OS estimates)

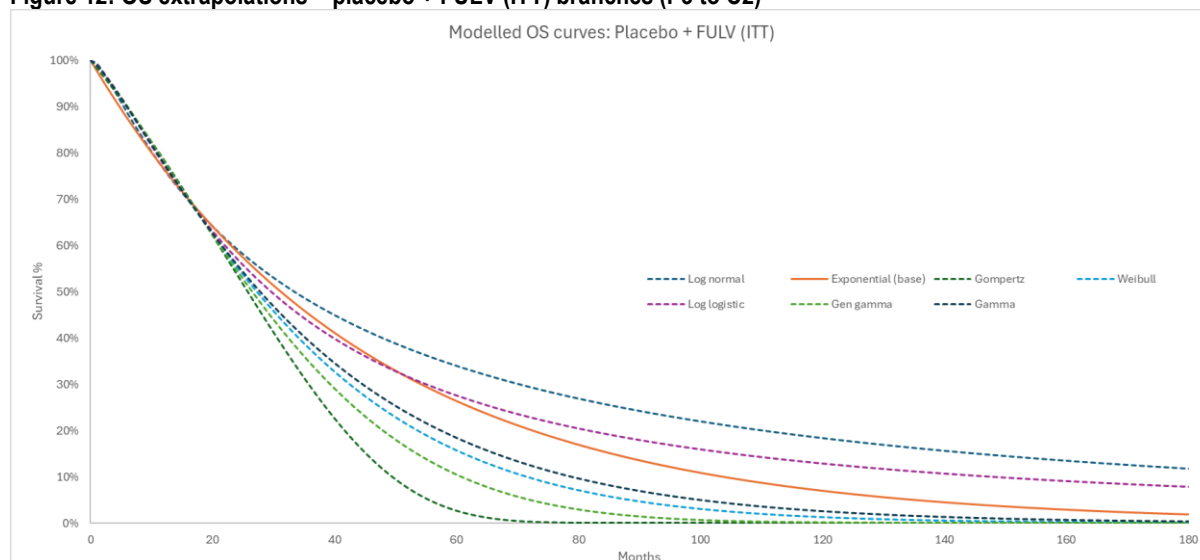
Bold values indicate lowest AIC and BIC among functions tested

- 6.65 Grinda 2021 presented a robust source for OS validation due to its large sample size and long follow-up. The landmark OS at 1-, 2-, and 3-years in Grinda 2021 were higher than all the CAPI+FULV (Altered) extrapolations, but the log normal, log logistic, generalised gamma, and exponential functions were relatively similar to the OS of Grinda 2021 at 5- and 10-years. The commentary acknowledged that the OS in patients treated with CAPI+FULV is potentially higher compared to the OS observed in Grinda 2021 given the evolving treatment landscape, in which the log normal and generalised gamma may be plausible options. However, interpretation of OS estimates after 2 years is limited by the immaturity of OS data in CAPItello-291.
- 6.66 The log normal function chosen as the base case for CAPI+FULV was the most optimistic OS extrapolation. Alternatively, the log logistic (second best AIC fit), generalised gamma, and exponential functions (second best BIC) showed more conservative OS estimates and may be more reasonable choices in the face of immature OS data and non-statistically significant OS results at DCO1 of CAPItello-291. Using the log logistic function led to a 66% increase in the ICER; the generalised gamma led to a 14% increase; and the exponential function led to a 60% increase.
- 6.67 The submission also presented a validation of the modelled OS in the placebo + FULV (ITT) branches against the OS estimates from placebo + FULV arms of the CONFIRM, PALOMA3, and FAKTION trials. CONFIRM (N=736) was a RCT that compared FULV 500

mg (n=230) to FULV 250 mg (n=239) in postmenopausal ER+ locally advanced or metastatic breast cancer following progression on an ET (2005-2007) and most patients received chemotherapy or ET as the first subsequent therapy. PALOMA3 (N=521) was an RCT that compared palbociclib + FULV (n=347) and placebo + FULV (174) in HR+/HER2- advanced breast cancer patients who had progressed after a previous ET (2013-2014) and most patients were heavily treated in the subsequent lines (49% [85/174] received three or more lines) including chemotherapy, ET, EVE, and CDK4/6 inhibitors. FAKTION (N=140) compared CAPI+FULV (n=69) and placebo + FULV (n=71) in postmenopausal women with ER+/HER2- locally advanced or metastatic breast cancer who had progressed on an ET (2015-2018) but subsequent therapies were not described. It was not clear why the Grinda 2021 study was not part of this validation despite Grinda 2021 being a substantially larger cohort with a longer follow-up compared to these trials.

- 6.68 The OS extrapolations for the placebo + FULV (ITT) branch are presented in Figure 12 and the AIC, BIC and landmark OS estimates from the extrapolations compared to the published trials/studies (including Grinda 2021) are presented in Table 15. AIC and BIC values were generally similar across functions, however the modelled OS estimates varied substantially across functions. For example, at 5-years the OS estimates ranged from 1.1% (Gompertz) to 29.8% (log normal).

Figure 12: OS extrapolations – placebo + FULV (ITT) branches (P3 to C2)



Source: constructed during the evaluation from 'Extrapolations placebo (ITT)' worksheet from the economic model
ITT = intention to treat; OS = overall survival

Table 15: Comparison of modelled OS for placebo + FULV (ITT) with the placebo + FULV arms from CONFIRM, PALOMA3, FAKTION, and Grinda 2021

Landmark OS	Placebo + FULV (ITT) in economic evaluation							Published trials/studies			
	Weibull	Gamma	Gompertz	Gen gamma	Log logistic	Log normal	Exp (base case)	CONFIRM (n=230)	PALOMA 3 (n=174)	FAKTION (n=71) ^a	Grinda 2021 (n=13590)
AIC	1036.4	1036.6	1037.2	1038.3	1037.5	1040.5	1040.2	-	-	-	-
BIC	1044.2	1044.3	1044.9	1049.9	1045.3	1048.3	1044.1	-	-	-	-
1 years	77.4%	77.4%	77.4%	78.3%	77.5%	77.4%	77.4%	74% ^b	84.4%	82.5%	~85%
2 years	50.1%	50.7%	47.7%	54.6%	57.1%	54.0%	53.0%	54% ^b	56.0%	42.5%	~70%
3 years	32.5%	34.2%	23.3%	34.5%	43.3%	43.0%	39.6%	38% ^b	38.7%	30.0%	~56%
5 years	12.3%	14.9%	1.1%	10.4%	27.5%	29.8%	22.0%	22% ^b	16.3%	9.6%	35.7%
10 years	0.7%	1.7%	0.0%	0.1%	12.8%	15.3%	5.0%	-	-	-	~12%
15 years	0.0%	0.2%	0.0%	0.0%	7.8%	9.2%	1.1%	-	-	-	-
Median OS	24 months	24 months	22.2 months	27 months	30 months	28.2 months	26.4 months	26.4 months	27.7 months	23.4 months	42.9 months

Source: Table 3.10, p203 and Table 3.11, p205 of the submission

AIC = Akaike information criterion; BIC = Bayesian information criterion; CDK4/6i = cyclin dependent kinase 4 and 6 inhibitor; ET = endocrine therapy; exp = exponential function; ITT = intention to treat; OS = overall survival

^a placebo + FULV arm from the ITT cohort of FAKTION

^b the submission stated these values were digitised from Figure 1 of Faslodex Product Information

Note: CONFIRM was in ET-experienced patients; and PALOMA3 and FAKTION were in CDK4/6 inhibitor-naïve patients

Italicised text indicated that the log logistic and gen gamma values and Grinda 2021 were added during the evaluation

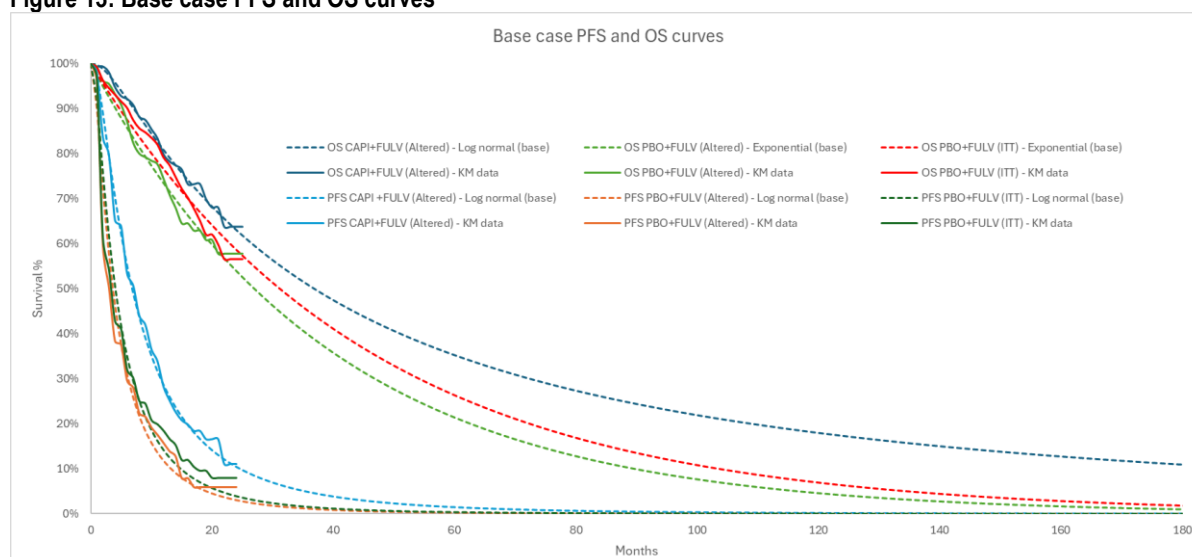
Bold values indicate lowest AIC and BIC among functions tested

6.69 The treatment landscape has evolved since these trials were conducted and subsequent therapies received in trials varied, which makes direct comparisons difficult. It is possible that patients treated with FULV monotherapy in the model may see a more optimistic long-term OS that is reflective of the evolving treatment landscape in the HR+/HER2- advanced setting. Among the parametric functions tested, the exponential function estimated OS which was much lower compared to Grinda 2021 and may have underestimated survival for the placebo + FULV (ITT) branches. Alternatively, the log normal and log logistic functions were more favourable for the placebo + FULV (ITT) branches; and the modelled OS estimates were more similar, albeit still considerably lower, compared to Grinda 2021. The choice of extrapolation function for OS in the placebo + FULV (ITT) branch was a key driver of the model. Applying the log normal function increased the ICER by 222%, and applying the log logistic increased the ICER by 40%.

6.70 The submission noted that since AKT pathway alteration is not a predictor of response to FULV monotherapy the extrapolation for the placebo + FULV (Altered) should be treated similarly to the placebo + FULV (ITT). The placebo + FULV (Altered) results were less favourable than the placebo + FULV (ITT) results, though this had negligible impact on the ICER. Using the placebo + FULV (ITT) results in branch P2 led to a <1% reduction in the ICER as branch P2 applied to only 0.45% of the model cohort.

6.71 The base case PFS and OS curves are presented in Figure 13.

Figure 13: Base case PFS and OS curves



Source: constructed during the evaluation using 'PFS KM data', 'OS KM data', 'Extrapolations CAPI (P1)', 'Extrapolations placebo (P2)', and 'Extrapolations placebo (ITT)' worksheets from the economic model

CAPI = capivasertib; FULV = fulvestrant; KM = Kaplan Meier; PBO = placebo; PFS = progression free survival; OS = overall survival

6.72 Overall, the modelling of OS was considered optimistic and favoured CAPI+FULV. The ESCs noted that the chosen functions resulted in increasing OS benefit over the 15 year time horizon, which was not reasonable. The lognormal function chosen for CAPI+FULV (Altered) was the most favourable long term OS extrapolation whereas the exponential function chosen for both placebo + FULV (ITT) and placebo + FULV (Altered) was less favourable than the loglogistic and lognormal functions. Further, the implied OS HR in the economic model (0.6 over 10 years) was also more favourable than in CAPItello-291 (OS HR = 0.69, 95% CI 0.45, 1.05) which did not report any statistically significant differences in OS between CAPI + FULV and placebo in the AKT pathway altered population. The OS extrapolations in the placebo + FULV (ITT) and CAPI+FULV (Altered) branches were key drivers of the model.

6.73 The submission stated the base case modelled OS HR of 0.60 over 10 years was in line with that observed in CAPItello-291 (OS HR = 0.69, 95% CI 0.45, 1.05). The ESCs agreed with the commentary that inferring a modelled OS benefit (HR=0.60 over 10 years) that was more favourable than the observed OS in CAPItello-291 was not reasonable and favoured CAPI+FULV. The PSCR stated that a HR approach (which produces convergence in OS over the 15-year time horizon) to modelling the OS gain might be more appropriate. The PSCR stated if the exponential is used to extrapolate OS for placebo + FULV, and a HR of 0.69 is used to generate the OS curve for CAPI+FULV, the ICER is \$115,000 to < \$135,000. The ESCs noted that use of alternative functions for the extrapolation of placebo + FULV OS were more conservative and resulted in convergence at earlier timepoints (~8 years). The ESCs considered that the modelled HR that was more favourable than the trial HR reflected the selection of favourable extrapolations for the CAPI+FULV arms and less favourable extrapolations for the placebo + FULV arms. The ESCs also considered that the sensitivity of the ICER to the

choice of function (and also the HR approach proposed in the PSCR) was indicative of the high level of uncertainty in the modelled benefits for the test + treatment. The ESCs considered that given the lack of demonstrated statistically significant difference in OS in CAPItello-291, and the potential impact of newly available subsequent therapies, it may not be reasonable for the model to include any OS difference, given the presented evidence.

- 6.74 The PF utility (0.784) was derived from the EQ-5D-5L data from CAPItello-291 and transformed using an Australian value set (Viney 2011). It was unclear why the more recent value set from Norman 2023 was not used or tested (which included responses from 4477 Australian adults using 500 choice triplets and represented a more comprehensive and contemporary data source than both Norman 2013 and Viney 2011).¹⁷ As such, the translation to utility from CAPItello-291 in the submission may not be based on the most appropriate value set available. The submission applied the same PF utility value in all treatment arms in the model based on the ITT cohort, as there were there were no clinically meaningful changes in global health status/QoL or any of the functional domains except for the role function domain at Cycle 15 for CAPI+FULV and Cycle 19 for placebo + FULV.
- 6.75 The PD utility (0.623) was derived from the average PD utility values from CAPItello-291 (using Viney 2011 algorithm) and external sources including from the literature (Lloyd 2006) and previous models considered by the PBAC in metastatic breast cancer Table 16. The submission considered the EQ-5D data in CAPItello-291 was not reliable to inform PD utilities due to low compliance and was skewed towards patients with better QoL.

Table 16: PD utility values used to calculate the PD utility value in the base case

CAPItello-291 (Viney 2011)	Lloyd 2006	Olaparib March 2023/ November 2023 ^a	Olaparib July 2024 ^b	Atezolizumab March 2021	Pembrolizumab March 2023	Sacituzumab govitecan July 2023 & November 2023	Average PD utility (base case)
0.748	0.512	0.678	0.53	0.583	0.703	July 2023: 0.605 ^c November 2023: 0.738 ^d	0.623 ^e 0.642 ^f

Source: Table 3.17, p214 of the submission

PD = progressed disease

^a Submission referred to the olaparib March 2023/November 2023 submissions as “OlympiA model (based on OlympiAD trial)”

^b Submission referred to the olaparib July 2024 submission as “OlympiAD model”

^c the values from Table 9 Sacituzumab govitecan PSD July 2023 PBAC Meeting are presented (note: these values were based on metastatic TNBC)

^d the values from paragraph 4.18, Sacituzumab govitecan PSD November 2023 PBAC Meeting are presented (note: these values were updated to reflect the trial-based utilities in HR+/HER2- metastatic breast cancer)

^e Average value included Sacituzumab govitecan July 2023 PD value (0.605)

^f Average value included Sacituzumab govitecan November 2023 PD value (0.738)

Italicised text indicates additional information included during the evaluation

¹⁷ Norman R, Mulhern B, Lancsar E, Lorgelly P, Ratcliffe J, Street D, Viney R. The Use of a Discrete Choice Experiment Including Both Duration and Dead for the Development of an EQ-5D-5L Value Set for Australia. *Pharmacoeconomics*. 2023 Apr;41(4):427-438. doi: 10.1007/s40273-023-01243-0. Epub 2023 Jan 31. PMID: 36720793; PMCID: PMC10020301

- 6.76 The utility values used in the PD average estimation had limited applicability to the HR+/HER2- locally advanced or metastatic breast cancer. Three of the PD utility values reported by the submission were based on TNBC patients (atezolizumab March 2021, pembrolizumab March 2023, and sacituzumab govitecan July 2023), and the PBAC has considered the TNBC patient population to not be applicable to the HR+ setting. The PD utility decrement from Lloyd 2006 may have reduced applicability to disease progression in current clinical practice. The PD utility values from the olaparib March 2023/November 2023 and July 2024 submissions were notably different (0.678 vs 0.53, respectively) thus potentially lacked face validity. The PD value from olaparib July 2024 was supposedly based on Lloyd 2006 however, this value was not verifiable. Nonetheless it may not have been reasonable to include two PD estimates based on Lloyd 2006 in the average PD estimate.
- 6.77 Despite the limitations in the CAPitello-291 data to inform the PD utility values, CAPitello-291 remains the most generalisable source and using the trial-based PD utility values is consistent with previous PBAC considerations (i.e., sacituzumab govitecan Public Summary Document [PSD], November 2023 PBAC Meeting). Applying the PD utility from CAPitello-291 (0.748) in the model led to an 11% decrease in the ICER. Though, it was questionable whether this indicated that the base case PD utility was 'conservative' because this decrease was driven by the assumed OS benefit between treatments which was unreasonable and likely overestimated. For example, when the log logistic function was applied to all OS curves (implicit modelled convergence, see Table 21) the ICER increased to \$255,000 to < \$355,000 per QALY gained; and additionally applying the PD utility from CAPitello-291 increased the ICER to \$255,000 to < \$355,000 per QALY gained (an additional 21% increase).
- 6.78 The submission assumed a testing cost of \$2,200; a 99% sensitivity/specificity; a 5% test failure rate; and testing uptake had reached the steady state of 95%. The submission did not consider re-testing costs for patients with an unknown test result or the associated cost of biopsy or re-biopsy and since the submission assumed a lower test failure rate than CAPitello-291 (15%), these costs are further underestimated. The submission also assumed testing occurred at diagnosis of metastatic disease and was not explicit with testing after disease progression, which potentially underestimates testing costs for patients who initially test negative but are eligible for a second test post-progression.
- 6.79 CAPI costs in branch P1 were informed by the time to treatment discontinuation (TTD) curve from CAPI+FULV (Altered) data extrapolated using the log normal function, resulting in a treatment duration of 10.6 months (including adjustment for 0.14 months of dose interruption). The log normal function was selected for consistency with the base case PFS curves, despite being the second lowest AIC/BIC function. The undiscounted CAPI cost per treatment course in true positive patients (branch P1) was \$| (discounted cost was \$|). The CAPI cost in false positives (branch P3) was \$| and was estimated by multiplying the cost per cycle of CAPI (\$|) by the median PFS (3.7 months) of the non AKT pathway altered subgroup who received placebo +

FULV in CAPItello-291. The commentary considered this was a crude assumption that did not consider discounting, nor did it represent the placebo + FULV ITT data which informed this branch. However, it is acknowledged that data to inform the treatment duration of false positive patients was not available and that this branch contributed to <1% of the proposed test scenario.

- 6.80 The model inappropriately applied an 86.2% RDI to CAPI costs (based on CAPItello-291). The proposed prices for the 200 mg and 160 mg tablets were identical and patients who have a dose reduction will be incurring the same cost for CAPI treatment regardless. In fact, there may be wastage costs that are not considered in the economic evaluation from dosage adjustments. Removing the RDI led to a 15% increase in the ICER. The ESCs considered that the treatment costs should be corrected to account for flat pricing for the two doses.
- 6.81 The model included grade 3/4 AEs that occurred in CAPItello-291 including, diarrhoea, rash, hyperglycaemia, and hypokalaemia. The submission assumed that 20% of these events required inpatient hospitalisation. The total cost per patient for treating AEs, based on CAPItello-291 (in the PF health state) was \$178 in the CAPI+FULV arm and \$6.50 in the FULV arm. The model was not sensitive to changes in AE management costs, disease monitoring costs, post-progression costs, or terminal care costs. The submission incorporated a once-off disutility due to grade 3/4 AEs in cycle 1 of the model and assumed a duration of three days.
- 6.82 The key drivers of the model are presented in Table 17.

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Table 17: Key drivers of the model

Description	Method/Value	Impact Base case: \$11/QALY gained
OS extrapolation of CAPI+FULV (Altered) branch P1	<p>The base case applied the log normal to extrapolate OS in the CAPI+FULV (Altered) branch P1.</p> <p>This was the most optimistic function. More conservative functions may be plausible given OS was immature and did not demonstrate a significant difference at DCO1 of CAPItello-291, such as the log logistic, exponential, and gen gamma</p>	<p>High, favours CAPI+FULV/test scenario</p> <p>Log logistic increased the ICER to \$122/QALY gained (+66%) Exponential increased the ICER to \$120/QALY gained (+60%) Gen gamma increased the ICER to \$124/QALY gained (+14%)</p>
OS extrapolation of PBO+FULV (ITT) branches P3-C2	<p>The base case applied the exponential to extrapolate OS in the PBO+FULV (ITT) branches (P3 to C2).</p> <p>This was considered pessimistic compared to OS observed in Grinda 2021 and alternative functions such as the log normal and log logistic were more similar to Grinda 2021.</p>	<p>High favours CAPI+FULV/test scenario</p> <p>Log normal increased the ICER to \$254/QALY gained (+222%) Log logistic increased the ICER to \$250/QALY gained (+40%)</p>
Time horizon	<p>The base case used a 15-year time horizon with no convergence assumed.</p> <p>The PBAC has previously accepted a 7-year time horizon in 2L HR+/HER2- locally advanced or metastatic breast cancer (Ribociclib July 2020/November 2020) and considered a 5-year time horizon in heavily pre-treated HR+/HER2- locally advanced or metastatic breast cancer (Sacituzumab govitecan July 2023)</p>	<p>High, favours CAPI+FULV/test scenario</p> <p>10-year time horizon increased the ICER to \$123/QALY gained (+29%) 7-year time horizon increased the ICER to \$122/QALY gained (+75%)</p>

Source: constructed during the evaluation using the economic model

CAPI = capivasertib; DCO1 = data cutoff 1; FULV = fulvestrant; HR+/HER2- = hormone receptor-positive/human epidermal growth factor receptor 2-negative; ICER = incremental cost effectiveness ratio; ITT = intention to treat; OS = overall survival; PBO = placebo; QALY = quality adjusted life years; 2L = second line setting.

The redacted values correspond to the following ranges:

- ¹ \$75,000 to < \$95,000
- ² \$135,000 to < \$155,000
- ³ \$95,000 to < \$115,000
- ⁴ \$255,000 to < \$355,000
- ⁵ \$115,000 to < \$135,000

6.83 The results of the stepped economic evaluation that compared the proposed test scenario with the no testing scenario are presented in Table 18.

Table 18: Results of the stepped economic evaluation

Step and component	Testing	No testing	Increment
Step 1: trial-based (22 months) costs and outcomes (undiscounted) ^a			
Costs ^b	\$	\$1,571	\$
Progression free survival years gained ^c	0.58	0.47	0.11
Incremental cost/extra progression free survival years gained			\$ ¹
Step 2: Include all costs + time horizon 15 years + transformed to LYG (discounted)			
Costs	\$	\$51,374	\$
LYG	3.34	2.91	0.43
Incremental cost/extra LYG gained			\$ ²
Step 3: cost per QALY gained over 15 years (discounted) - base case			
Costs	\$	\$51,374	\$
QALY gained	2.19	1.90	0.29
Incremental cost/extra QALY gained			\$ ³

Source: 'Trial-based analysis' worksheet from the economic model; Table 3.35 p229; Table 3.36, p229 of the submission

CAPi = capivasertib; FULV = fulvestrant; LYG = life years gained; PBO = placebo; QALYs = quality adjusted life years

^a Costs include AKT testing, CAPi treatment, FULV treatment, and AE management costs and were from 'Trial-based analysis' worksheet from the economic model and setting the discount rate to 0% and time horizon to 22 months.

^b The trial-based analysis costs were calculated from 'Trial-based analysis' worksheet and weighted using the proportion of patients in each test branch from the 'Model outline' worksheet from the economic model.

^c The trial-based analysis progression free survival years gained were calculated from 'Trial-based analysis' worksheet and weighted using the proportion of patients in each test branch from the 'Model outline' worksheet from the economic model.

The redacted values correspond to the following ranges:

¹ \$155,000 to < \$255,000

² \$55,000 to < \$75,000

³ \$75,000 to < \$95,000

6.84 In addition, the results that compared the AKT pathway altered populations in the proposed test scenario (branches P1, P2 and P5) and the no testing scenario (branch C1) are presented in Table 19.

Table 19: Results based on the AKT pathway altered populations in the proposed test scenario (branches P1, P2, and P5) and the no testing scenario (branch C1)

Cost per QALY gained over 15 years (discounted) - AKT pathway altered			
	CAPi + FULV	PBO	Increment
Costs	\$	\$51,374	\$
QALY gained	2.48	1.90	0.59
Incremental cost/extra QALY gained			\$ ¹

Source: constructed during the evaluation using 'Model outline' worksheets from the economic model, assuming 100% prevalence of alteration, and accounting for additional testing costs in non altered patients (\$4,400 total).

CAPi = capivasertib; FULV = fulvestrant; LYG = life years gained; PBO = placebo; QALYs = quality adjusted life years

Italicised text indicates calculation conducted during the evaluation

The redacted values correspond to the following ranges:

¹ \$75,000 to < \$95,000

6.85 The disaggregated results from the economic evaluation are presented in Table 20.

Table 20: Disaggregated costs and outcomes (discounted)

Costs	Testing						No testing			Inc (Test vs no test)	% of total Inc
	Total	P1 (TP)	P2 (FN)	P4 (FP)	P4 (TN)	P5-P6 (TF) ^a	Total	C1	C2		
% per branch	-	44.7%	0.45%	0.45%	44.7%	4.9%	-	50%	50%	-	-
Capivasertib and placebo	\$█	\$█	\$█	\$█	\$█	\$█	\$█	\$█	\$█	\$█	█%
Fulvestrant	\$█	\$█	\$█	\$█	\$█	\$█	\$█	\$█	\$█	\$█	█%
Subsequent anti-cancer therapies	\$11,229	\$4,352	\$56	\$56	\$5,553	\$1,212	\$12,430	\$6,215	\$6,215	-\$1,200	█%
Surgery/radiotherapy post recurrence	\$267	\$119	\$1	\$1	\$120	\$26	\$269	\$134	\$134	-\$1	█%
Adverse events management	\$84	\$80	\$0	\$0	\$3	\$1	\$7	\$3	\$3	\$78	█%
Adverse events from subsequent treatments	\$344	\$152	\$2	\$2	\$154	\$34	\$345	\$173	\$173	-\$2	█%
Disease monitoring	\$15,000	\$7,777	\$53	\$59	\$5,837	\$1,274	\$13,065	\$6,532	\$6,532	\$1,935	█%
Terminal care	\$22,679	\$9,568	\$109	\$107	\$10,585	\$2,310	\$23,695	\$11,847	\$11,847	-\$1,015	█%
Testing costs	\$2,004 ^b	\$983	\$10	\$10	\$983	\$19 ^b	\$0	\$0	\$0	\$2,004	█%
Total	\$█	\$█	\$█	\$█	\$█	\$█	\$█	\$█	\$█	\$█	100%
LYG											
PF	0.67	0.38	0.00	0.00	0.23	0.05	0.52	0.26	0.26	0.15	34.4%
PD	2.67	1.35	0.01	0.01	1.07	0.23	2.39	1.19	1.19	0.28	65.6%
Total LYG	3.34	1.73	0.01	0.01	1.30	0.28	2.91	1.46	1.46	0.43	100%
QALY gained											
PF	0.53	0.30	0.00	0.00	0.18	0.04	0.41	0.41	0.41	0.12	39.7%
PD	1.66	0.84	0.01	0.01	0.66	0.15	1.49	1.49	1.49	0.18	60.3%
Total QALY gained	2.19	1.14	0.01	0.01	0.85	0.18	1.90	1.90	1.90	0.29	100%

Source: Constructed during the evaluation using 'ICER'; 'model outline'; 'Trace – CAPI (P1)'; 'Trace – placebo (P2)'; and 'Trace – placebo (ITT)' worksheets from the economic model

CAPI = capivasertib; FN = false negative; FP = false positive; FULV = fulvestrant; LYG = life year gained; PBO = placebo; PD = progressed disease PF = progression free; QALYs = quality adjusted life years; TP = true positive; TN = true negative; TF = test failure

^a Branches P5, and P6 were treated identically (same costs and outcomes)

^b The total testing cost in the proposed test scenario is the sum of testing costs in branches P1-P6 + cost of test failures that incur an MBS fee (\$18.81)

Note: the costs and outcomes in each branch were weighted by the proportion of patients in each branch

Italicised text indicates additions made during the evaluation

6.86 The base case ICER was \$75,000 to < \$95,000 per QALY gained. The ICER was primarily driven by the higher incremental cost of CAPI in the proposed test scenario compared to the comparator scenario (\$█, ~█% of total incremental costs); and the greater time spent in the PD health state in the proposed test scenario compared to the comparator scenario (0.28 incremental LYG, ~66% total incremental LYG). Costs and outcomes in the test scenario predominantly were incurred in branches P1 (true positive) and P4 (true negative) as the model assumed the majority of patients

occupied these branches. Testing costs only contributed to 1% of total incremental costs, however, as noted above testing costs were potentially underestimated.

- 6.87 The results of key univariate and multivariate sensitivity analyses are summarised in Table 21.

Table 21: Sensitivity analyses conducted by the submission and additional analyses during the evaluation

		Inc QALY	Inc cost	ICER	%Δ
-	Base case	0.29	\$█	\$█ ¹	-
-	Discount rate 0% (base case 5%)	0.41	\$█	\$█ ²	-█%
-	Discount rate 3.5% (base case 5%)	0.32	\$█	\$█ ¹	-█%
-	Time horizon 10 years (base case 15 years)	0.22	\$█	\$█ ³	+█%
-	PD utility = 0.748 CAPItello-291 (base case 0.623)	0.33	\$█	\$█ ¹	-█%
Univariate sensitivity analyses					
OS extrapolation – PBO + FULV (base case exponential)					
#1	OS PBO + FULV (ITT) = log logistic	0.21	\$█	\$█ ⁴	+█%
#2	OS PBO + FULV (ITT) = log normal	0.09	\$█	\$█ ⁵	+█%
OS extrapolation – CAPI+FULV (base case log normal)					
#3	OS CAPI+FULV (Altered) = exponential	0.18	\$█	\$█ ⁶	+█%
#4	OS CAPI+FULV (Altered) = log logistic	0.17	\$█	\$█ ⁶	+█%
#5	OS CAPI+FULV (Altered) = gen gamma	0.26	\$█	\$█ ³	+█%
Time horizon (base case 15 years)					
#6	Time horizon 7 years	0.16	\$█	\$█ ⁶	+█%
RDI (base case 86.2%)					
#7	100% RDI (base case 86.2% RDI)	0.29	\$█	\$█ ³	+█%
Multivariate/scenario analyses					
A1	PD utility 0.748 + time horizon 10 years + 100% RDI	0.24	\$█	\$█ ⁴	+█%
B1	OS extrapolation all branches = log normal	0.09	\$█	\$█ ⁵	+█%
C1	OS extrapolation all branches = log logistic	0.09	\$█	\$█ ⁵	+█%
D1	OS CAPI+FULV (Altered) = log normal (base case) + OS PBO+FULV (ITT) = log logistic + OS PBO+FULV (Altered) = log logistic	0.21	\$█	\$█ ⁴	+█%
E1	A1 + B1	0.09	\$█	\$█ ⁵	+█%
F1	A1 + C1	0.08	\$█	\$█ ⁵	+█%
G1	A1 + D1	0.19	\$█	\$█ ⁶	+█%
H1	A1 + OS CAPI+FULV (Altered) = log logistic (second best AIC) + OS PBO+FULV (ITT) = exponential (base case) + OS PBO+FULV (Altered) = exponential (base case)	0.13	\$█	\$█ ⁷	+█%
PSCR scenario using HR approach					
	PSCR scenario – applied OS HR of 0.69 to placebo+FULV (P2) and applied exponential function to placebo+FULV (P2) and placebo + FULV (ITT) branches	0.21	\$█	\$█ ⁴	+█%
	PSCR scenario as above but applied Weibull function	0.20	\$█	\$█ ⁴	+█%
	PSCR scenario as above but applied Gamma function	0.19	\$█	\$█ ⁴	+█%
Multivariate analyses conducted for ESC					
	PSCR HR approach (exponential function) Time horizon 10 years, Test failure rate 15%, 100% RDI	0.17	\$█	\$█ ⁶	+█%

Source: constructed during the evaluation using Table 3.40, pp232-3 of the submission and the economic model

HR = hazard ratio; ICER = incremental cost effectiveness ratio (\$/QALY gained); Inc = incremental; ITT = intention to treat; OS = overall survival; PBO = placebo; PD = progressive disease; QALY = quality adjusted life year; RDI = relative dose intensity; TTD = time to treatment discontinuation; %Δ = percentage change from base case ICER

Multivariate sensitivity: A1: Set Cell B6 = 0.748 in 'Utilities' worksheet + Cell B11 = 100% in 'Drug costs' worksheet + Cell B9 = 10 'Assumptions' worksheet

The redacted values correspond to the following ranges:

- ¹ \$75,000 to < \$95,000
- ² \$55,000 to < \$75,000
- ³ \$95,000 to < \$115,000
- ⁴ \$115,000 to < \$135,000
- ⁵ \$255,000 to < \$355,000
- ⁶ \$135,000 to < \$155,000

⁷ \$155,000 to < \$255,000

6.88 Overall, the ICER was potentially underestimated given that:

- The base case OS extrapolations modelled a continuing OS benefit over the 15-year time horizon in favour of CAPI+FULV/test scenario compared to placebo + FULV/comparator test scenario. This was optimistic given:
- No statistically significant OS benefit was observed in CAPItello-291 at DCO1 (OS HR = 0.69, 95% CI 0.45, 1.05) and as such it may not be reasonable to model any OS differences. The implied OS HR in the economic model (OS HR = 0.60 over 10 years) was actually more optimistic than the HR in CAPItello-291.
- No convergence of OS was assumed to address any uncertainties with long term extrapolation (median follow up 14.9 in the CAPI+FULV arm and 14.3 in the placebo + FULV arm months in CAPItello-291, extrapolated out to 15 years).
- Any longer-term OS benefit may be reduced given the evolving treatment landscape for HR+/HER2- locally advanced or metastatic breast cancer.
- The 15-year time horizon was relatively long compared to previous PBAC considerations in similar patient populations (7-year time horizon was accepted in the PBAC's consideration of ribociclib November 2020; and 5-year time horizon was considered in the PBAC's consideration of sacituzumab govitecan July 2023)
- The submission inappropriately applied an RDI of 86.2% to CAPI drug costs despite the proposed price for CAPI for the 200 mg and 160 mg strength tablets being the same.

6.89 In a scenario analysis conducted during the evaluation (see scenario A1, Table 21) applying trial-based PD utility using the algorithm by Viney 2011 (0.748), a 100% RDI, and a 10-year time horizon increased the ICER to \$115,000 to < \$135,000 per QALY gained (+1%). Additional scenarios (E1, F1, G1 and H1) applied scenario A1 and additionally varied the OS extrapolations in the CAPI+FULV (Altered) branch or placebo + FULV (ITT) and placebo + FULV (Altered) branches and further increased the ICERs.

6.90 It was likely that the model will become less sensitive to these changes if OS convergence and/or a shorter time horizon was assumed, which would provide more conservative estimates, reduce the uncertainty around extrapolations and also create a more robust base case QALY. The ESCs considered that an additional multivariate sensitivity analysis, which corrected CAPI drug costs, applying the following inputs would also be informative:

- A HR approach with convergence over 15 years.
- A reduced time horizon of 10 years.
- Increased test failure rate of 15%.

The ESCs noted that this analysis resulted in an ICER of \$135,000 to < \$155,000 per QALY.

- 6.91 The ESCs also considered it would be useful to consider a sensitivity analysis using the PBO+FULV unknown AKT pathway status subgroup data for health outcomes in model branches P5 and P6. However, the ESCs noted that this was not possible using the model provided with the submission as it did not include KM data for the unknown AKT pathway status subgroup.
- 6.92 As discussed in paragraph 6.50, given the uncertainty in excluding the complement subgroup (i.e., non-positive AKT pathway altered patients) from treatment with CAPI+FULV, a scenario analysis was conducted during the evaluation that assumed no testing, with CAPI+FULV available to all patients irrespective of biomarker status.
- 6.93 The non-biomarker selected scenario analysis assumed no testing and that all inputs were informed by the ITT cohort for CAPI+FULV and placebo + FULV arms. The placebo + FULV ITT extrapolations and inputs remained unchanged from the base case settings (i.e., extrapolated PFS using log normal and OS using exponential). For the CAPI+FULV ITT arm the parametric distributions with the best AIC/BIC statistics and upholding visual plausibility were used; the gen gamma and log logistic were selected to extrapolate PFS and OS, respectively. The results of key sensitivity analyses in the non-biomarker selected population are shown in Table 22.

Table 22: Scenario analysis results – non-biomarker population

		Inc LYG	Inc QALY	Inc cost	ICER	% Δ
-	Base case (biomarker selected)	0.43	0.29	\$	\$ ¹	-
I1	CAPI + FULV (ITT) PFS = gen gamma; OS = log logistic	0.67	0.48	\$	\$ ²	+ %
I2	CAPI + FULV (ITT) PFS = log normal	0.67	0.45	\$	\$ ²	+ %
I3	CAPI + FULV (ITT) OS = exponential	0.32	0.26	\$	\$ ³	+ %
I4	I1 + time horizon 10 years	0.48	0.36	\$	\$ ⁴	+ %
I5	I4 + RDI 100%	0.48	0.36	\$	\$ ³	+ %
I6	I5 + trial-based PD utility 0.748	0.48	0.38	\$	\$ ³	+ %

Source: constructed during the evaluation using the economic model and Attachment 3.2 to the submission

AIC = Akaike information criterion; BIC = Bayesian information criterion; CAPI = capivasertib; FULV = fulvestrant; Inc = incremental; ICER = incremental cost effectiveness ratio; LYG = life year gained; PBO = placebo; QALYs = quality adjusted life years; % Δ = percentage change from the submission's base case ICER

I1: assumed no testing (including associated testing costs); efficacy was informed by CAPI+FULV arm from ITT data (including extrapolations); extrapolations selected according to best AIC/BIC fit (PFS = gen gamma and OS = log logistic)

I2: same as I1 except PFS extrapolation = log normal

I3: same as I1 except OS extrapolation = exponential (despite being the last ranked AIC/BIC fit, this extrapolation produced an OS curve with convergence and did not cross over with the placebo + FULV base case extrapolations).

I4: same as I1 and additionally set the time horizon to 10 years

I5: same as I4 and additionally set RDI = 100% (Cell B12 = 100%, 'Drug costs' worksheet)

I6: same as I5 and additionally applied the trial-based PD utility value (Cell B6 = 0.748, 'Utilities' worksheet)

The redacted values correspond to the following ranges:

¹ \$75,000 to < \$95,000

² \$95,000 to < \$115,000

³ \$135,000 to < \$155,000

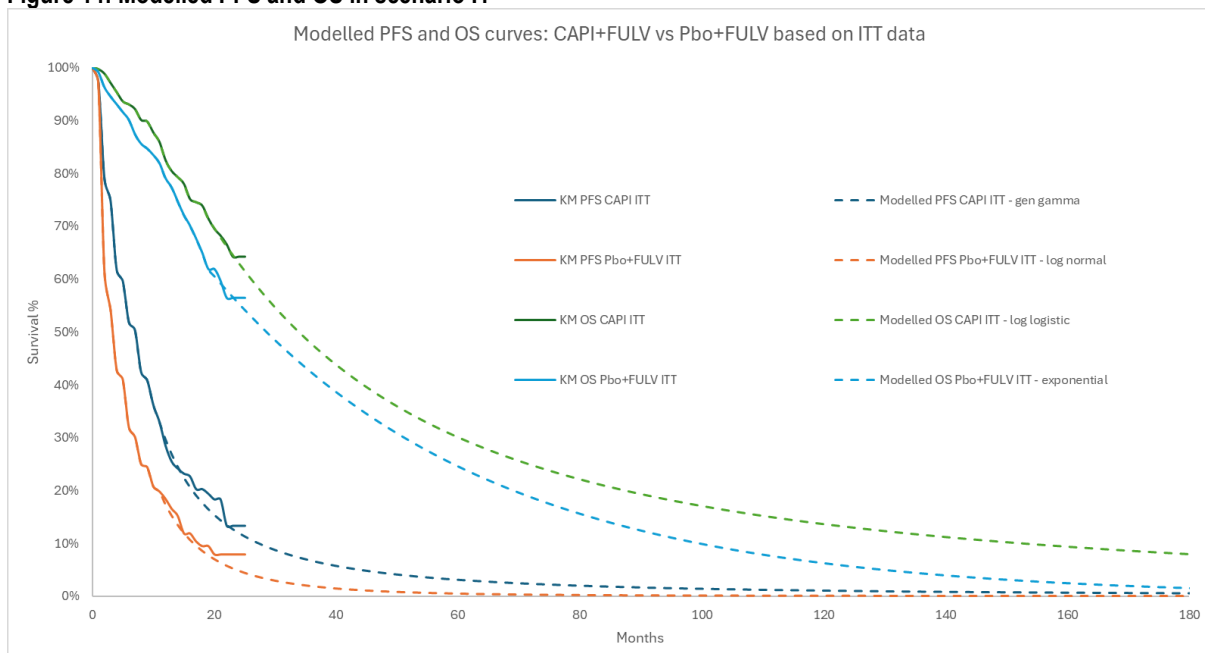
⁴ \$155,000 to < \$255,000

- 6.94 Assuming no testing and patients are treated with CAPI irrespective of biomarker status and applying the best statistically fitting curves led to a 1% increase in the base case ICER (from \$75,000 to < \$95,000 to \$95,000 to < \$115,000 per QALY gained;

scenario I1). Under this scenario CAPI is received in 100% of the ‘intervention arm’ rather than only ~45% in the proposed test scenario base case and the ITT results showed a benefit in all patients treated with CAPI+FULV (0.93 LYG in the scenario vs 0.67 LYG in the base case). This increased the cost of CAPI treatment in the scenario analysis compared to the base case (\$| vs \$|) and was accompanied by a greater QALY gain (0.48 vs 0.29 incremental QALY gain). However, given other assumptions remain unchanged from the submission’s base case, this ICER was likely underestimated for the same reasons as described in paragraph 6.88.

6.95 Assuming scenario analysis I1 as representative of treating non-biomarker selected patients, the resulting modelled PFS and OS curves are presented in Figure 14.

Figure 14: Modelled PFS and OS in scenario I1



Source: constructed during the evaluation using ‘Extrapolations CAPI (P1)’ and ‘Extrapolations CAPI ITT’ worksheets from the economic model and Attachment 3.2 to the submission

CAPI = capivasertib; FULV = fulvestrant; ITT = intention to treat; PFS = progression free survival; OS = overall survival

Note: extrapolation selected base on best statistical AIC/BIC fit and visual plausibility

Drug cost/patient/course

Table 23: Drug cost per patient for proposed and comparator drugs

	Proposed drug Trial dose and duration	Proposed drug Model	Proposed drug Financial estimates	Comparator Trial dose and duration	Comparator Model	Comparator Financial estimates
Mean cycles received	8.7 cycles	11.52 cycles	11.48 cycles	5.9 cycles	5.45 cycles	-
Mean duration	5.9 months ^a	10.6 months ^b	10.6 months	2.7 months ^a	5.9 months	-
Cost/patient/course						
True positives	-	\$ [REDACTED] / \$ [REDACTED] ^c	\$ [REDACTED] / \$ [REDACTED] ^{c, d}	-	\$1,564 ^e	-
False negative	-	\$ [REDACTED] / \$ [REDACTED] ^c		-		-
False positives	-	\$ [REDACTED] / \$ [REDACTED] ^c		-		-
True negative	-	\$ [REDACTED] / \$ [REDACTED] ^c		-		-
Unknown	-	\$ [REDACTED] / \$ [REDACTED] ^c		-		-

Source: Table 2.47, pp117-8 of the submission; Table 14.3.1.4.3, CAPItello-291 CSR

CAPi = capivasertib; CSR = Clinical Study Report; DPMQ = dispensed price for maximum quantity; FULV = fulvestrant

^a Actual dose intensity in the trial = total treatment duration minus the total duration of dose interruptions

^b Mean treatment duration in the model accounting for dose interruptions.

^c read as CAPI cost / FULV cost

^d Calculated as the DPMQ x scripts per treatment course (CAPI: \$ [REDACTED] x 11.48 scripts per treatment; FULV: \$226.71 x 10.59 scripts per treatment).

^e FULV cost only

Note: Mean dose of treatment was not reported in the trial or model, instead the mean number of treatment cycles received in the AKT pathway altered population was presented.

6.96 The cost of CAPI per patient per course assuming the mean treatment duration of 10.6 months and 86.2% RDI in the model in patients who have a true positive test for AKT pathway alterations was \$ [REDACTED] (\$ [REDACTED] if 100% RDI) in the economic model. In comparison the cost of CAPI per treatment course in the financial estimates for the same treatment duration (10.6 months) assuming 100% RDI was \$ [REDACTED]. The cost of CAPI in false positive patients, assuming a duration of 3.7 months and no RDI applied, was \$ [REDACTED] in the economic model, however this was a crude calculation as treatment duration for these patients is unknown (see also para 6.79) and the financial estimates assumed a treatment duration of 10.6 months for all patients treated with CAPI.

Estimated PBS & financial implications

6.97 The submission adopted an epidemiological approach to estimate the financial impact of testing for AKT pathway alterations (*PIK3CA*, *AKT1*, or *PTEN*) and treatment with CAPI+FULV in HR+/HER2- locally advanced or metastatic breast cancer patients following disease progression or recurrence on or after an ET with or without a CDK4/6 inhibitor.

6.98 The key inputs and sources are presented in Table 24.

Table 24: Key inputs for financial estimates

Data	Value and source	Comment
Eligible population		
BC incidence	The submission obtained the BC incidences from the AIHW Cancer in Australia 2021 report (Table S3.4 'Cancer in Australia Chapter 3 – Cancer projections and Australia's ageing population' data table).	DUSC agreed with the commentary that this was reasonable.

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Data	Value and source	Comment
% Stage III-IV BC	The submission estimated the proportion of Stage I-IV BC (including unknown) based on the AIHW Australian Cancer Database 2014. The submission calculated the proportion of advanced or metastatic BC with an adjustment for unknown patients (17.68%)	DUSC agreed with the commentary that this was reasonable. The approach for adjusting for unknown patients was also accepted by the PBAC and DUSC for olaparib (Table 20, olaparib PSD, March 2023 PBAC Meeting).
% HR+/HER2- subtype	The proportion of HR+/HER2- subtype was 70%. The submission stated that this proportion was accepted by the PBAC in its consideration of sacituzumab govitecan in July 2023.	DUSC agreed with the commentary that this was reasonable. This was noted to be consistent with previous submissions to the PBAC (fulvestrant PSD, July 2020 PBAC Meeting; and abemaciclib PSD, March 2022 PBAC Meeting) and also confirmed by the SEER data.
% Test positive to AKT pathway alteration	The proportion of BC patients who test positive to AKT pathway alterations was 50%. The submission stated AKT pathway hyperactivation occurs in up to 50% of patients and presented the prevalence rates from several studies in the financial workbook (Khoury 2020, Stemke-Hale 2008; Cancer Genome Atlas Network 2012; Mosele 2020; and Chung 2017). The submission also cited comments from the PASC who noted that around 50% of BC tumours will have an AKT pathway alteration (p8, 1766 Ratified PICO Confirmation, April 2024 PASC Meeting).	The prevalence of AKT pathway alterations reported in the publications cited by the submission (38-43%) were lower than the 50% used in the base. Estimates from the literature based only on HR+/HER2- advanced/ metastatic BC identified during the evaluation (Mosele 2020, Chung 2017, Park 2024, and CAPItello-291) ranged between 40.8% and 59.8%. DUSC considered the prevalence was uncertain in the Australian setting and likely overestimated in the submission. The prevalence of 50% was not adjusted for test performance. Testing in CAPItello-291: 289/708 = 40.8% positive 419/708 = 59.2% negative (includes 92 patients with inconclusive results)
Test uptake rate	The submission assumed a gradual uptake rate of █████% in Year 1 that increases to █████% in Year 6. The submission assumed uptake rate would be similar to BRCA testing that was used in the submission for Olaparib in November 2023.	Test uptake rate in Year 1 and 2 may be underestimated considering that testing in breast cancer patients is common practice.
HR+/HER2- locally advanced or metastatic on 1L CDK4/6i	The submission based the number of HR+/HER2- locally advanced or metastatic BC patients treated in the 1L with a CDK4/6i on DUSC estimates of CDK4/6i use. The submission stated that DUSC applied a 2% annual growth rate. The submission (p238) stated this estimation was based on Sacituzumab govitecan PSD July 2023 and Trastuzumab deruxtecan November PSD November 2023. The submission assumed that the proportion of patients who did not receive a CDK4/6i in the 1L could be eligible for CAPI+FULV in the 1L setting.	Sourcing 1L CDK4/6i use from DUSC was reasonable, however, the 2025 to 2030 estimates could not be verified or reproduced during the evaluation. DUSC considered that the number of patients seems to be overestimated by applying an annual growth rate of approximately 3.5%. DUSC considered that it would be appropriate to base this step on the numbers of patients progressing on adjuvant CDK4/6i, noting that based on the TDxD submission of 2023, the number of patients was 50 for every year.
% Patients who progress from 1L to 2L treatment	The proportion of patients who progress from 1L to 2L setting = 88%. The submission stated this was based on the KARMA registry (Wong 2022). KARMA was established in August 2019 as a study of Australian patients who received 1L combination treatment of ribociclib and an AI, where ribociclib was obtained	The submission assumed that of the patients on 1L CDK4/6i, 88% will progress and be eligible for CAPI in the 2L. The requested restriction allows for testing and treatment any time after disease progression on or after an ET. As such, patients in the 3L+ setting would also be eligible for testing and CAPI+FULV. Omission of patients from the 3L+ who have not had

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Data	Value and source	Comment									
	<p>through a medicines accept program between May 2017 and June 2018. This access program included postmenopausal women with HR+/HER2-metastatic BC who had not received prior systemic treatment in the metastatic setting. Wong 2022 (N=160) reported that of the 74 patients who had disease progression on 1L ribociclib + AI, 65 patients (88%) received a 2L therapy. The mean age of patients in the registry was 54.3 years.</p>	<p>CDK4/6i may potentially underestimate the financial estimates. DUSC agreed with commentary that this assumption was underestimated as patients in the 3L+ setting would also be eligible for testing and CAPI+FULV. In the CAPItello trial 24.9% of patients received CAPI+FULV in the 3L or 4L setting. DUSC considered that most patients with mBC will still be relatively fit for consideration of 3L+ options.</p>									
Grand-fathered	<p>The submission included █1 grandfathered patients. No details were provided.</p>	<p>The submission did not include grandfathered patients as part of financial estimates from testing as they were likely to have already been tested. The financial workbook assumed all grandfathered patients were treated for a mean duration of 10.6 months.</p>									
Utilisation											
CAPI scripts	<p>The submission's estimated total number of scripts of CAPI per patient per treatment course = 11.48 packs. A 'compliance rate' of 88.27% (322.41/365.25 days) was multiplied by 13 packs. The submission stated that the mean treatment duration of 322.41 days or 10.6 months was from the Altered subgroup of CAPItello-291 at DCO1.</p>	<p>The submission estimated the mean treatment duration of 10.6 months from the economic model and accounting for dose interruptions (0.14 months) rather than from CAPItello-291 at DCO1. The 'compliance rate' in the financial model however is not the same as the RDI and was actually just an adjustment to reduce patient years from 12 months to 10.6 months. In the base case of the financial estimates, appropriately a 100% RDI was assumed (given the adjusted duration).</p>									
CAPI cost	<p>The proposed price of CAPI (200 mg and 160 mg) per 64 pack is presented in the table below.</p> <table border="1" data-bbox="352 1272 775 1373"> <thead> <tr> <th></th> <th>AEMP</th> <th>DPMQ</th> </tr> </thead> <tbody> <tr> <td>Published</td> <td>\$10,687.80</td> <td>\$10,849.93</td> </tr> <tr> <td>Effective</td> <td>\$█</td> <td>\$█</td> </tr> </tbody> </table> <p>Note: one pack = 64 tablets, one pack required for one month supply.</p>		AEMP	DPMQ	Published	\$10,687.80	\$10,849.93	Effective	\$█	\$█	<p>The submission proposed the same price for the 200 mg and 160 mg tablets.</p>
	AEMP	DPMQ									
Published	\$10,687.80	\$10,849.93									
Effective	\$█	\$█									
CAPI uptake rate	<p>The submission assumed that the uptake rate in 1L was █% and in the 2L setting █% from Year 1 to Year 6.</p>	<p>As patients would only get tested for AKT pathway alteration if they were willing or wanting to use CAPI a high uptake rate among patients who test positive may be reasonable as the uptake rate of testing was already accounted for. The commentary and DUSC considered an uptake rate of 95% in 1L and 100% in the 2L setting was reasonable.</p>									
MBS items	<p>The proposed MBS fee for AKT pathway testing was \$2,200 per test. The submission applied the 85% MBS rebate (\$1,870).</p>	<p>Acknowledging the MBS item descriptor allows one test per primary tumour diagnosis, it was not clear how patients with an unknown test result would be handled in practice or if retesting could occur in patients who initially test negative but develop an alteration after disease progression. It is possible these scenarios could lead to out-of-pocket cost to patients and present a potential equity issue.</p>									

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Data	Value and source	Comment
		The submission did not apply the Greatest Permissible Gap (\$98.70) to the MBS rebate. This underestimated the MBS costs. The MBS rebate applying the Greatest Permissible Gap was \$2,101.30.
Cost offsets	The submission only included cost offsets for the MBS costs, there were no cost offsets for PBS/RPBS items. A cost offset was calculated assuming that 10% of patients will receive AKT pathway testing from Year 1 to Year 6 in absence of an MBS-funded test.	<p>The basis for claiming that 10% of patients would already know their AKT pathway alteration status was unclear, however DUSC considered it was reasonable to assume that some patients would already know of their disease status. The estimation of number of tests in 2L patients (after CDK4/6i) was overestimated as the submission did not consider that only the 88% of patients who progress from 1L to 2L would be tested.</p> <p>The submission did not include cost offsets associated with PBS listing of CAPI. This may be reasonable as cost offsets would not be realised if therapies are displaced to later lines.</p>

Source: constructed using information from Section 4.1 to 4.3 of the submission

AI = aromatase inhibitor; AIHW = Australian Institute of Health and Welfare; AEMP = approved ex-manufacturer's price; ARTG = Australian Register of Therapeutic Goods; BC= breast cancer; CAPI = capivasertib; CDK4/6i = Cyclin-dependent kinases 4 and 6 inhibitor; CGP = comprehensive genomic profiling; DPMQ = dispensed price for maximum quantity; DUSC = Drug Utilisation Sub Committee; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ET = endocrine therapy; FULV = fulvestrant; HR+ = hormone positive; HER2- = Human epidermal growth factor receptor 2 negative; KARMA = Kisqali Access Registry for Metastatic breast cancer in Australia; NGS = Next Generation Sequencing; PASC = PICO Advisory Sub-Committee; para = paragraph; PBS = Pharmaceutical Benefits Scheme; PSD = public summary document; pts = patients; SOC = standard of care; RPBS = Repatriation Pharmaceutical Benefits Scheme; 1L = first line; 2L = second line

The redacted values correspond to the following ranges:

¹ < 500

6.99 The number of patients eligible for testing and treatment with CAPI and the net cost to the PBS/RPBS, MBS, and health budget is presented in Table 25. In the submission there was no adjustment to account for the fact that only 88% of patients will progress from 1L to 2L and therefore be tested for treatment in the 2L setting. Values in Table 25 include correction of the number of patients who progress from 1L to 2L.

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Table 25: Estimated use and financial implications

	Value	2025	2026	2027	2028	2029	2030
A1	BC incidence	-	1	1	1	1	1
A2	Stage III/IV BC (17.7%)	A1×17.7%	2	2	2	2	2
A3	HR+/HER2- subtype (70%)	A2×70%	2	2	2	2	2
Pts eligible for 1L treatment							
B1	Pts on 1L CDK4/6i	DUSC estimates	2	2	2	2	2
B2	Pt not eligible for 1L CDK4/6i	A3–B1	2	2	3	3	3
B3	Test uptake rate (1L tested population)	B2×█-% ^a	3	3	3	3	3
B4	Pts assumed to have been tested already	B2×█%	3	3	3	3	3
B5	% Test positive (50%)	B3×50%	3	3	3	3	3
B6	Treatment uptake rate (█%) (1L treated population)	B5×█%	3	3	3	3	3
Pts eligible for 2L treatment (incorporates 88% of patients who progress from 1L to 2L)							
C1	Pts who progress from 1L to 2L after CDK4/6i (88%)	B1×88%	2	2	2	2	2
C2	Test uptake rate (2L tested population)	C1×█-% ^a	2	2	2	2	2
C3	Pts assumed to have been tested already	C1×█%	3	3	3	3	3
C4	% Test positive (50%)	C2×50%	3	2	2	2	2
C5	Treatment uptake rate (█%) (2L treated population)	C3×█%	3	2	2	2	2
D1	Grandfathered pts (Treated population)	-	3	3	3	3	3
Total tested and treated population							
E1	Total tested population ^b	B3+C2	2	2	2	2	2
E4	Total treated population	B6+C4+D1	2	2	2	2	2
Net cost MBS (incorporated 88% who progress from 1L to 2L) – used for H1							
F1	Cost of testing	E1×\$1,870 ^c	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4
F2	Cost offset ^d	(B4+C3) ×\$1,870	-\$ 5	-\$ 5	-\$ 5	-\$ 5	-\$ 5
F3	Net cost MBS	F1+F2	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4
Net cost PBS/RPBS							
-	Total scripts – CAPI	-	6	7	7	7	7
-	Total scripts – FULV	-	6	6	7	7	7
G1	Net cost PBS/RPBS – CAPI	Includes co-payment	\$ 8	\$ 9	\$ 10	\$ 10	\$ 11
G2	Net cost PBS/RPBS – FULV	Includes co-payment	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4
G3	Net cost PBS/RPBS	G1+G2	\$ 8	\$ 9	\$ 10	\$ 11	\$ 11
Net cost to the health budget							
H1	Net health impact that incorporates 88% pts who progress from 1L to 2L	F3+G3	\$ 8	\$ 9	\$ 11	\$ 11	\$ 11

Source: constructed from 'Calculation' worksheet of the financial workbook, Table 4.21 and 4.22, p251 of the submission, Sheet 7, financial estimates spreadsheet, Attachment 4.1 to the submission

BC= breast cancer; CDK4/6i = Cyclin-dependent kinases 4 and 6 inhibitor; DUSC = Drug Utilisation Sub Committee; HR+ = hormone positive; HER2- = Human epidermal growth factor receptor 2 negative; pts = patients; 1L = first line; 2L = second line

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a Test uptake rates: ■% Year 1, ■% Year 2, ■% Year 3-6

b The total test population presented in E1 are the total tested patients in the 1L and 2L that incorporated the proportion of patients who progressed from 1L to 2L (88%). The submission did not include this proportion in its estimation of the tested population.

c Calculated as the total pts eligible for testing multiplied by \$1,870. The submission applied the 85% rebate (testing fee = \$1,870) and did not apply the Greatest Permissible Gap (\$98.70).

d the cost offset to the MBS assumed that ■% of patients eligible for testing in 1L and 2L (e.g., ■% x 500 to < 5,000 = < 500 pts in 1L and ■% x 500 to < 5,000 = < 500 pts in 2L in Year 1 assumed to have tested already).

Note: the submission assumed that grandfathered patients were not tested again and enter as part of the treated population

The redacted values correspond to the following ranges:

¹ 20,000 to < 30,000

² 500 to < 5,000

³ < 500

⁴ \$0 to < \$10 million

⁵ net cost saving

⁶ 5,000 to < 10,000

⁷ 10,000 to < 20,000

⁸ \$40 million to < \$50 million

⁹ \$50 million to < \$60 million

¹⁰ \$70 million to < \$80 million

¹¹ \$80 million to < \$90 million

6.100 When the eligible patient population was revised to incorporate the 88% of patients who progress from the 1L to 2L setting, the total cost to the MBS was \$0 to < \$10 million in Year 1, increasing to \$0 to < \$10 million in Year 6; the total cost to the PBS/RPBS was \$40 million to < \$50 million in Year 1, increasing to \$80 million to < \$90 million in year 6; and the net impact on the health budget was \$40 million to < \$50 million in Year 1, increasing to \$80 million to < \$90 million in Year 6.

6.101 Table 26 contains further revisions considered appropriate by DUSC:

- The increase in patients on 1L CDK4/6i (B1) has been revised from 3.5% to 2% per annum.
- The uptake rate (1L tested population)(B3) has been revised from |% Year 1, |% Year 2, |% Year 3-6 in the submission to |% Years 1&2, |% Year 3, |% Year 4&5, |% Year 6.
- The proportion who test positive has been revised from 50% in the submission to 38%.
- Patients who progress from 1L to 2L after CDK4/6i (88%) (C1) are reduced because the patients on 1L CDK4/6i (B1) were reduced.
- The test uptake rate (2L population)(C2) and proportion who test positive (C4) have been revised in the same way as the 1L population.
- Patients progressing from 2L to 3L have been included. In the CAPItello-291 trial 24.9% of patients received CAPI+FULV in the 3L or 4L setting. DUSC considered most patients with mBC will still be relatively fit for consideration of 3L+ options.

Table 26: DUSC revision of patients scripts and costs to PBS for capivasertib

	2025	2026	2027	2028	2029	2030
1L patients treated	1	1	1	1	1	1
2L patients treated	2	2	2	2	2	2
3L+ patients treated^a	1	1	1	1	1	1
Grandfathered patients	1	1	1	1	1	1
Total scripts – CAPI	3	3	3	4	4	4
Total scripts – FULV	3	3	3	4	4	4
Net cost PBS/RPBS – CAPI	\$ 5	\$ 6	\$ 5	\$ 7	\$ 7	\$ 8
Net cost PBS/RPBS – FULV	\$ 9	\$ 9	\$ 9	\$ 9	\$ 9	\$ 9
Net cost PBS/RPBS	\$ 5	\$ 5	\$ 5	\$ 7	\$ 8	\$ 8

^a incorporates 25% of patients who progress from 2L to 3L

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ 5,000 to < 10,000

⁴ 10,000 to < 20,000

⁵ \$50 million to < \$60 million

⁶ \$40 million to < \$50 million

⁷ \$60 million to < \$70 million

⁸ \$70 million to < \$80 million

⁹ \$0 to < \$10 million

6.102 Overall, DUSC considered financial estimates for the PBS/RPBS to be overestimated due to overestimation of the positive test rate and overestimation of the growth rate in the number of patients on 1L CDK4/6 inhibitors. Costs for FULV are also likely to be overestimated as no offsets were included for patients who would otherwise be treated with FULV monotherapy.

Quality use of medicines

6.103 The submission stated that an educational diagnostic program will inform on the collection of ideal tumour sample to ensure the quality and DNA profile of tumour extraction can be properly assessed by radiologists, surgeons, oncologists and pathologists; and would collaborate with healthcare professionals to ensure appropriate use of CAPI+FULV that is in line with the clinical evidence and TGA indication.

Financial management – risk sharing arrangements

6.104 The submission stated that the sponsor is willing to enter into a risk-sharing arrangement but did not describe details of addressing the uncertainty in the submission.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend capivasertib for treatment of hormone receptor positive (HR+) human epidermal growth factor receptor 2 negative (HER2-) locally advanced unresectable or metastatic breast cancer with evidence of a serine/threonine protein kinase (AKT) pathway alteration, following recurrence or progression on or after endocrine therapy. The PBAC noted that as an integrated codependent submission, the proposed MBS item for AKT pathway testing would be considered at the November 2024 MSAC meeting. The PBAC noted that there was a moderate clinical benefit for capivasertib (CAPI) compared with fulvestrant (FULV) in terms of progression free survival, but no demonstrated improvement in overall survival. The PBAC considered that the clinical benefit in practice is likely to be further reduced as, for many patients, FULV is not the most appropriate comparator and other more effective treatments would be preferred. The PBAC also noted inferior safety with increased risk of clinically significant grade 1-2 adverse events including hyperglycaemia, rash, and diarrhoea. The PBAC considered that the incremental cost-effectiveness ratio was high at the proposed price, and likely to be underestimated due to optimistic assumptions in the model, particularly the inclusion of an overall survival benefit for CAPI and due to use of FULV as the comparator.
- 7.2 The primary reason for this outcome was due to the economic evaluation.
- 7.3 The PBAC considered that the restriction wording should be aligned with the CAPItello-291 trial population and specify that the condition is estrogen-receptor (ER) positive. The PBAC also considered that the restriction should align with the CAPItello-291 trial inclusion criteria with respect to prior treatments. The PBAC noted that 69% of patients in CAPItello-291 had received a prior CDK4/6 inhibitor and most patients will receive a CDK4/6 inhibitor in the 1L metastatic setting (77% from Australian ARORA registry). However, the PBAC considered that it would be reasonable to leave this to clinical decision making rather than specifying that patients must have received prior CDK4/6 inhibitor treatment. The PBAC noted that the majority of patients enrolled in CAPItello-291 (76%) had received endocrine therapy (ET) in the locally advanced/metastatic setting. However, under the requested restrictions it was possible to initiate CAPI+FULV at any stage in the advanced or metastatic setting. The PBAC considered that, given the changing treatment landscape, and likelihood that some patients would receive ET/CDK4/6 inhibitors treatment as adjuvant treatment for early breast cancer, it was not necessary for the restrictions to specify the treatment line, consistent with the CAPItello-291 trial. However, the PBAC noted that the use of CAPI+FULV beyond 2L would limit the applicability of FULV as the comparator. The PBAC considered that the proposed criterion “treatment must be following recurrence or progression on or after endocrine therapy” should be amended to “treatment must be following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing endocrine-based adjuvant therapy” to more closely align with the CAPItello-291 inclusion criteria.

- 7.4 The PBAC considered there was a moderate clinical need for additional effective therapies in HR+/HER2- locally advanced unresectable or metastatic breast cancer and that the proposed clinical place for CAPI+FULV was reasonable, but the Committee noted that there are several other 2L and later treatment options that may be preferred over CAPI+FULV, given the limitations of the comparative evidence.
- 7.5 The PBAC considered that although the nominated comparator of FULV monotherapy was a relevant 2L therapy, on its own it was not representative of SOC in the 2L+ setting. The PBAC considered that other more efficacious treatment options may be preferred over FULV monotherapy in clinical practice; these include olaparib (in patients with BRCA+ tumours), trastuzumab deruxtecan (in patients with HER2 low tumours), everolimus+exemestane/FULV/tamoxifen combinations, or chemotherapy. The PBAC noted that 25% of patients in CAPItelo-291 were treated in the 3L+ setting. The PBAC considered that FULV monotherapy would also not be the preferred SOC treatment for patients in the 3L+ setting, where alternative therapies that were not previously used in the 2L could be used. The PBAC considered that the use of FULV monotherapy as the sole comparator introduced uncertainty as to the relative benefit and cost-effectiveness of CAPI+FULV in clinical practice. The PBAC acknowledged identifying an alternative single main comparator was difficult and considered a mixed comparator would be a better representation of SOC in clinical practice.
- 7.6 The submission was based on one head-to-head trial comparing CAPI+FULV to placebo + FULV: CAPItello-291 (N=708). Another trial comparing CAPI+FULV to placebo + FULV (FAKTION) was available, however the PBAC noted that the sample size for FAKTION was substantially smaller (N=140). The PBAC noted that in CAPItello-291 there was a statistically significant PFS improvement in the CAPI+FULV arm compared to the placebo + FULV arm in the ITT cohort (HR=0.60, 95% CI 0.51, 0.71, $p < 0.001$, median PFS difference 3.6 months) and the AKT pathway altered subgroup (HR=0.50, 95% CI: 0.38-0.65, $p < 0.001$, median PFS difference 4.2 months). There was also a trend to PFS favouring CAPI+FULV over placebo + FULV in the non AKT pathway including unknown status (HR=0.70, 95% CI 0.56, 0.88). The PBAC noted that there was a trend to a small PFS benefit in the known non-AKT pathway altered subgroup (HR=0.79, 95% CI 0.61-1.02) but a substantial difference in PFS for the unknown AKT status subgroup (HR=0.52, 95% CI 0.32, 0.83), suggesting that the results for the ITT population were driven by both the known AKT altered and unknown subgroups. The PBAC considered that the results of the test for interaction between the AKT pathway altered and known non-altered subgroups supported targeting of treatment to patients with AKT pathway alterations, who are most likely to benefit from treatment, although noted that the results were equivocal when patients with unknown AKT status were included in the complement.
- 7.7 The PBAC noted that OS data from CAPItello-291 were immature (only 24.5% [87/355] and 30.6% [108/353] of patients had an OS event at DCO1 in the CAPI+FULV and placebo + FULV arms, respectively) and no significant differences were demonstrated. The PBAC noted that the pre-PBAC response indicated updated OS data from the

interim analysis from CAPItello-291 (DCO2) were received by the sponsor, but were not provided with the pre-PBAC response and were not available at the time of PBAC's consideration. The PBAC considered that any incremental OS benefit at later DCOs may be reduced given the availability of later line treatments and the evolving treatment landscape in HR+/HER2- advanced breast cancer and considered that the updated OS data from CAPItello-291 are likely to be informative with respect to the magnitude of longer-term OS benefit associated with CAPI+FULV.

- 7.8 Overall, the PBAC considered the claim of superior PFS in AKT pathway altered patients treated with CAPI+FULV was adequately supported, based on the comparison to placebo + FULV. However, the magnitude of PFS benefit in CAPItello-291 is likely to overestimate the benefit in Australian clinical practice because the comparator of FULV is not representative of SOC. The PBAC agreed with the ESCs and commentary that indirect treatment comparisons of CAPI+FULV with chemotherapy, olaparib or T-DXd as well as near market comparators would be unlikely to provide reliable estimates of comparative benefit. Nonetheless, the comparative treatment effect from CAPItello-291 was not representative of the relative benefit of CAPI+FULV in clinical practice, providing overly optimistic outcomes in favour of CAPI+FULV.
- 7.9 The PBAC noted that adverse events (AEs) were significantly increased in the CAPI+FULV arm compared to the placebo + FULV arm in the CAPItello-291 and FAKTION trials. In CAPItello-291, the CAPI+FULV arm had a higher proportion of serious AEs (16.1% vs 8%), Grade ≥ 3 AEs (42.8% vs 15.7%) and AEs leading to discontinuation (13% vs 2.3%). The PBAC also noted a significant increase in AEs of interest (any grade) for patients treated with CAPI, including: hyperglycaemia (17% vs 4%, and requiring insulin in 5%) which was persistent in around half of patients (28/60), rash (38% vs 7%), and diarrhoea (72% vs 20%) which was associated with risk of acute kidney injury due to dehydration. The PBAC considered these to be clinically meaningful in the context of a chronic oral therapy with an expected median duration of therapy of 10 months and signified a substantial level of toxicity associated with CAPI. Further, the PBAC considered that there is a potentially higher risk of AEs associated with CAPI in practice in patients with poorer performance status and/or comorbidities. The PBAC considered that the claim of inferior comparative safety for CAPI was reasonable but considered that it was not meaningful to describe the safety of CAPI as "manageable".
- 7.10 The PBAC considered that the AEs outlined above are a significant quality use of medicines issue, and requested that the sponsor develops an educational program for prescribing clinicians and relevant nurses regarding monitoring and management of hyperglycaemia, diarrhoea and rash. The PBAC felt it was important to highlight the concerns of the TGA delegate that (i) insulin may not be effective, (ii) there is a potential drug-drug interaction with metformin, and (iii) use of antidiabetic medications carries a risk of hypoglycaemia on days where capivasertib is not administered. The PBAC noted comments in the TGA delegate overview that the

optimal management strategy for management of hyperglycaemia was not clear, and requested the sponsor advise how this will be addressed.

- 7.11 The PBAC noted the integrated codependent submission requested: 1) a new MBS item for AKT pathway testing (for *PIK3CA*, *AKT1* and *PTEN* gene variants) to determine access to CAPI on the PBS, and 2) the PBS listing of CAPI for the treatment of HR+/HER2- locally advanced unresectable or metastatic breast cancer with evidence of an AKT pathway alteration. The PBAC noted that the proposed PBS population (patients with AKT pathway alterations) was narrower than the TGA indication for CAPI, but was consistent with FDA, CDA and EMA indications. The PBAC considered that the claim of codependency between CAPI and AKT pathway testing remained somewhat unclear. Although results from CAPItello-291 and tests for interaction suggested AKT pathway alteration was predictive of PFS benefit for CAPI treatment when compared to known non AKT pathway status (excluding all patients with an unknown AKT alteration test result), this was not observed when compared to all patients without a positive AKT pathway alteration test result (including unknown status). While acknowledging the uncertainties regarding AKT pathway testing, the PBAC considered that it would be preferable to target treatment to patients most likely to benefit from CAPI+FULV given the potential safety concerns associated with CAPI. The PBAC noted that consideration of the proposed MBS item for AKT pathway testing was a matter for MSAC consideration.
- 7.12 The PBAC noted the submission presented a modelled economic evaluation, based on results from CAPItello-291, comparing the proposed test scenario (NGS tumour tissue testing for the detection of AKT pathway alterations [*PIK3CA*, *AKT1*, or *PTEN*]) and treatment with CAPI+FULV for patients with AKT pathway alterations, with the comparator test scenario (no testing) and treatment with FULV for all patients. The PBAC noted that the base case 15-year time horizon was relatively longer than previous PBAC considerations in similar populations (5-10 years) and was based on data with median follow up was 14.3-14.9 months in CAPItello-291. Applying a 10-year time horizon increased the ICER by 29%. In addition, the base case OS extrapolations modelled a continuing, increasing OS benefit over the 15-year time horizon which was optimistic since no statistically significant OS benefit was observed in the AKT pathway altered subgroup in CAPItello-291 at DCO1. The PBAC noted the high level of variation in the ICER depending on the approach to extrapolation of OS curves for CAPI+FULV and FULV and considered the modelled OS benefit introduced substantial uncertainty in the estimates of cost-effectiveness. The PBAC considered that it was not clear whether there is likely to be any OS benefit for CAPI in the longer term, given the potential impact of newly available subsequent therapies. Although data with additional follow-up from CAPItello-291 (DCO2) may help to inform the modelled benefit, these data were not available at the time of PBAC consideration and the PBAC considered that it is unclear whether these data will reflect subsequent therapies used in clinical practice.

- 7.13 The PBAC noted that AEs were included in the economic evaluation, however these were limited to grade ≥ 3 AEs of diarrhoea, rash, hyperglycaemia and hypokalaemia, assuming 20% of patients were hospitalised, and disutilities were only assumed to apply for 3 days per 28 day cycle. The PBAC considered that the model was likely to have underestimated the cost and disutility for AEs associated with CAPI. The PBAC considered that the economic analysis should include the cost of monitoring for hyperglycaemia (which in the TGA PI is initially recommended every 2 weeks), and the cost of medications and medical consultations for grade 1-2 adverse events of hyperglycaemia, rash and diarrhoea; noting that there would also likely be significant out of pocket costs to patients relating to over the counter costs of medications and medical consultations (e.g. dermatology) for management of these AEs.
- 7.14 The PBAC also noted that the submission inappropriately applied an RDI of 86.2% to CAPI drug costs despite the proposed price for CAPI for the 200 mg and 160 mg strength tablets being the same, which underestimated the cost for CAPI.
- 7.15 The PBAC noted that in the submission base case the ICER was \$75,000 to < \$95,000/QALY gained. The PBAC considered the ICER was high and likely to be underestimated, primarily due to the optimistic assumptions in the model of OS benefit over a 15 year time horizon, which were not supported by the evidence presented. The PBAC also noted that underestimation of CAPI costs, and underestimation of AE costs and disutilities also contributed to underestimation of the ICER. Further, the PBAC considered that using FULV monotherapy as the comparator treatment did not reflect clinical practice as it does not fully represent the established SOC in the 1L or 2L+ setting. The incremental benefit for CAPI+FULV in the economic model is therefore potentially overestimated compared to clinical practice. The PBAC advised an acceptable ICER in this population would be no more than \$45,000/QALY gained, consistent with what was advised for sacituzumab govitecan in 3L unresectable locally advanced or metastatic HR+/HER2- breast cancer (paragraph 5.11, sacituzumab PSD, November 2023 PBAC meeting) and trastuzumab deruxtecan in HER2 low unresectable or metastatic breast cancer (paragraph 7.10, T-DXd PSD, November 2023 PBAC meeting), and given the moderate clinical need, moderate potential benefit and inferior safety profile of CAPI+FULV.
- 7.16 The PBAC noted the submission adopted an epidemiological approach to estimate the financial impact of testing for AKT pathway alterations (*PIK3CA*, *AKT1*, or *PTEN*) and treatment with CAPI+FULV in the requested population. When the eligible patient population was revised to incorporate the 88% of patients who progress from the 1L to 2L setting, the total cost to the PBS/RPBS was \$40 million to < \$50 million in Year 1, increasing to \$80 million to < \$90 million in year 6; and the net impact on the health budget was \$40 million to < \$50 million in Year 1, increasing to \$80 million to < \$90 million in Year 6. The PBAC considered the financial estimates for the PBS/RPBS to be overestimated due to overestimation of the positive test rate and overestimation of the growth rate in the number of patients on 1L CDK4/6 inhibitors. Costs for FULV are also likely to be overestimated as no offsets were included for

patients who would otherwise be treated with FULV monotherapy. The PBAC also considered that the addition of grandfathered patients was not appropriate as they would be captured in the prevalent population. The PBAC considered that although some patients may access treatment in 3L or later, the number was uncertain and would only be a proportion of patients who chose not to take up treatment with CAPI in 1L or 2L.

7.17 The PBAC considered a resubmission for capivasertib should address the following issues:

- Provide a revised economic evaluation incorporating: adjustment of the incremental benefit for CAPI to account for a mixed comparator representative of standard of care, updated data with additional follow-up from CAPItello-291, conservative assumptions for extrapolation of OS, revised costs and disutilities for AEs including grade 1-2 AEs, and correction of costs for CAPI.
- Reduction of the cost of CAPI to give an ICER of no more than \$45,000 per QALY with changes to the economic evaluation as outlined above.
- Revised financial estimates with changes as per paragraph 7.16.

The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

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

Outcome:

Not recommended

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

The sponsor had no comment.