NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Lutetium-177 vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Lutetium-177 vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]

Contents:

The following documents are made available to consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the Draft Guidance from** Novartis
   a. Responses to EAG questions
   b. Responses to EAG queries

3. **Consultee and commentator comments on the Draft Guidance Document** from:
   a. British Nuclear Medicine Society (BNMS)*
      **endorsed by the Royal College of Physicians*
   b. British Uro-oncology Group (BUG)
   c. Prostate Cancer UK

4. **Comments on the Draft Guidance Document from experts:**
   a. Dr Stephen Allen, nominated by Tackle Prostate Cancer

5. **Comments on the Draft Guidance Document received through the NICE website**

6. **External Assessment Group critique of company response to the DG**

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

Appraisal title

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee (company)	Advanced Accelerator Applications	**Summary** Advanced Accelerator Applications have presented detailed responses to address the Committee's remaining key areas of uncertainty, as well as a revised economic base case and supporting scenario analyses as requested by the Committee. The Committee recognised the considerable unmet need associated with metastatic castration-resistant prostate cancer (mCRPC) in patients having previously received treatment with androgen receptor pathway inhibitors (ARPIs) and taxane-based chemotherapy, or who are medically unsuitable for taxanes. This unmet need is multifaceted, with patients facing a poor prognosis and limited treatment options. Clinical experts further noted during both Appraisal Committee Meetings (ACMs) that the primary treatment option at this stage of disease, cabazitaxel, is associated with debilitating side effects. ^{177}Lu vipivotide tetraxetan represents the first PSMA-targeted radioligand therapy to receive marketing authorisation for the treatment of prostate cancer, offering a targeted approach to treatment able to improve survival benefits with a tolerable safety profile. The Committee heard from patient representatives having received ^{177}Lu vipivotide tetraxetan following receipt of prior taxanes, and the vast improvement in quality of life (QoL) they felt following receipt of ^{177}Lu vipivotide tetraxetan, compared to prior taxane-based	Thank you for your comment. The committee considered the consultation response from the company. Please see responses to individual issues below.

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			therapy.[1] In this response to the second Appraisal Consultation Document (ACD2), the Company has provided detailed responses to address the Committee's key areas of uncertainty surrounding the Company's submission: • The suitability of the Company's network meta-analysis (NMA) to inform the relative efficacy of ^{177}Lu vipivotide tetraxetan and the principal comparator, cabazitaxel • The use of real-world evidence (RWE) to estimate relative treatment effects in overall survival (OS) between cabazitaxel and ^{177}Lu vipivotide tetraxetan • A thorough re-analysis of the RWE is being undertaken, in order to further resolve committee uncertainty surrounding the use of RWE data to inform treatment effect in the model • The unavailability of robust data to inform the comparison between ^{177}Lu vipivotide tetraxetan and standard of care (SOC) in the population of patients for whom taxanes are medically unsuitable • The exclusion of radium-223 as a comparator in the Company submission • The Company's estimates of health-state utility values associated with each of the treatments considered in the economic analysis The NICE Committee have stated they have not yet seen their preferred analysis using real-world evidence for OS for cabazitaxel as a reference group for the absolute event estimates, and applying the hazard ratio (HR) for the relative	

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			effect on OS between ^{177}Lu vipivotide tetraxetan and cabazitaxel from the ERG-preferred NMA to estimate OS for ^{177}Lu vipivotide tetraxetan. Clinical experts question the plausibility of this approach, as the difference between predicted OS and radiographic progression-free survival (rPFS) for ^{177}Lu vipivotide tetraxetan seem implausible given the mismatch in data sources (rPFS for ^{177}Lu vipivotide tetraxetan is still based on direct trial data from the VISION trial). Fundamentally this approach relies on a biased treatment effect for cabazitaxel informed by the CARD study. CARD results do not reflect UK practice, in which ARPI sequencing is not endorsed by NHS commissioning due to the lack of evidence of clinical benefit of such practice. Furthermore, the CARD trial exclusively enrolled patients who had progressed *within 12 months* on a prior ARPI, which is likely to be a treatment effect modifier. As confirmed by clinical expert feedback, patients who had progressed within 12 months of ARPI treatment were likely to have developed ARPI resistance and would show poor outcomes with receipt of a second ARPI, thereby biasing relative treatment effect towards cabazitaxel.[2] The biased hazard ratio from the ERG-preferred NMA therefore does not reflect the relative treatment effect between ^{177}Lu vipivotide tetraxetan and cabazitaxel that is anticipated in the population who would be eligible for ^{177}Lu vipivotide tetraxetan in UK clinical practice .[2] Seven UK clinical experts gave their opinions during a recent virtual advisory board meeting, experts are unanimous in their opinion that ^{177}Lu vipivotide tetraxetan is predicted to offer patients longer survival than cabazitaxel. Following the first Appraisal Committee Meeting (ACM), the Committee concluded that both the Company and ERG NMAs comparing ^{177}Lu vipivotide tetraxetan with cabazitaxel were associated with high uncertainty due to heterogeneity across the included trials, and that further exploratory analyses were	

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			required to resolve uncertainty. Following the second ACM, the Committee favoured the ERG's analysis where trials that exclusively enrolled ARPI-naïve patients were excluded, because previous ARPI treatment is likely to be a treatment effect modifier. However, the trials included in the ERG's NMA (VISION, CARD and TheraP) were unchanged between the first and second Committee meetings, and thus these analyses remain subject to high uncertainty and are inappropriate, as outlined later in the response to Key Issue 1 below. The ERG further noted that timing of progression on a prior ARPI may be a treatment effect modifier for response to cabazitaxel, as evidenced by a real-world study conducted by Watson *et al.* (2022).[3] The CARD trial exclusively enrolled patients who had progressed within 12 months of initiating a prior ARPI;[4] patients in the VISION trial had received a prior ARPI, but there were no criteria relating to the duration of response prior to progression. Importantly, only a small proportion (~[redacted]%) of patients in VISION were reported to have progressed within 12 months of initiating a prior ARPI.[5] The ERG and NICE Committee acknowledged that the timing of progression on a prior ARPI is likely a treatment effect modifier, and thus the treatment effects derived from VISION and CARD are not comparable. On this basis, clinical experts strongly disagreed with CARD's inclusion in the NMAs as it is biases the hazard ratio and is not reflective of UK practice.[6] Furthermore, as per the Watson *et al.* (2022) study, only 68.1% of the mCRPC patient population (n=592) had disease progression within 12 months of initiating their first ARPI treatment.[3] As such, the CARD trial fails to account for one-third of the mCRPC patient population and its results are not reflective of real-world clinical practice.	

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			In order to present the Committee with the analyses requested, the Company has provided the following analyses: • In line with Committee preferences, the OS estimates for cabazitaxel derived from the RWE study have been used as the reference, to which a hazard ratio (HR) has been applied to derive OS estimates for ^{177}Lu vipivotide tetraxetan, including HRs derived from the ERG-preferred NMA. • In line with Committee preferences, trials that enrolled exclusively ARPI-naïve patients were excluded from the indirect treatment comparisons (ITC) informing relative efficacy between ^{177}Lu vipivotide tetraxetan and cabazitaxel. • ITCs focused on the CARD trial and the subpopulation of patients who received ARPI as part of SOC in both VISION treatment arms, in line with the EAG's preferences. However, given timing of progression on a prior ARPI has been shown to be an important treatment effect modifier for sequential ARPI treatment, the ARPI-SOC arm of VISION and the control arm of CARD do not form a true common comparator, and the results of these ITCs are biased in favour of the cabazitaxel. To reduce heterogeneity and resulting bias in the ITC, the following additional analyses were explored: o A Bucher ITC was conducted between the CARD and a subgroup of the VISION trial who met the eligibility criterion of the CARD trial: patients having progressed *within 12 months of receipt of a prior ARPI*, who are likely to have developed rapid ARPI resistance. This approach aims to directly	

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			address the heterogeneity between the trials forming the basis of networks proposed by both the Company and EAG, namely VISION and CARD. However, this analysis is limited by breaking of randomisation and small number patient numbers in the VISION subgroup. o Given the remaining limitations associated with the Bucher ITC, it is challenging to estimate comparable relative effects between the interventions of interest (^{177}Lu vipivotide tetraxetan and cabazitaxel) and a second ARPI. Therefore, an unanchored matching adjusted indirect comparison (MAIC) was performed between the intervention arms of the CARD and VISION trials, adjusting for differences in key prognostic variables and treatment effect modifiers. This analysis presents various advantages and has been incorporated in the Company's revised base case. o Further details of the Bucher ITC and unanchored MAIC are provided in the response to Key Issue 1 below, as well as **Error! Reference source not found.** and **Error! Reference source not found.**. These analyses both offer further evidence for ^{177}Lu vipivotide tetraxetan's superior treatment efficacy over cabazitaxel (see response to Key Issue 1). The Company also reiterates the importance and relevance of the RWE analysis previously presented in the original submission particularly as it addresses the key concerns with using an NMA informed by a trial subject to selection bias and not reflective of UK clinical practice. In line with the principles detailed in the NICE real-world evidence	

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			framework,[7] the UK RWE study would provide estimates of relative treatment effects representative of clinical practice. In order to address the committee and EAG's concerns and further improve the reliability of the UK RWE as a source of relative efficacy for ^{177}Lu vipivotide tetraxetan and cabazitaxel in the model, the Company is conducting a re-analysis of the PSW originally performed, selecting patients from the RWE dataset who meet key eligibility criteria from the VISION trial, and aiming to adjust for a greater number of prognostic factors and treatment effect modifiers (as identified from a systematic literature review [SLR] of prognostic factors and confirmed through clinical expert feedback).[8] The results of this re-analysis are unfortunately not yet available for inclusion in the Company response. The Company however expects the results to more closely reflect UK practice, in line with clinical expert opinion and corroborate those of the Bucher ITC and unanchored MAIC detailed in this response, providing the Committee with further evidence of improved survival with ^{177}Lu vipivotide as compared to cabazitaxel. This analysis will be shared with the Committee when available in order to provide all relevant information to make an informed decision on the relative treatment effect. The revised base case and additional scenario analyses presented demonstrate that treatment with ^{177}Lu vipivotide tetraxetan extends life over 3 months. In the revised company base case, median OS is estimated to be [redacted] months for ^{177}Lu vipivotide tetraxetan compared to [redacted] months for cabazitaxel, and incremental life years gained (LYG) are estimated to be [redacted], thus ^{177}Lu vipivotide tetraxetan meets the NICE end-of-life criteria. The updated base case is associated with an incremental cost-effectiveness ratio (ICER) versus cabazitaxel below the willingness-to-pay (WTP) threshold of £50,000 for medicines which reach the end-of-life criteria and thus demonstrates ^{177}Lu	

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<tr><td></td><td></td><td></td><td>vipivotide tetraxetan to be a cost-effective use of NHS resources. The Company has additionally explored scenarios to address remaining uncertainty which provide validation for the base case approach.

The Company therefore strongly urges the Committee to reconsider the best approach to inform the relative treatment effect, given the issues highlighted in the ITCs previously considered, the results of the newly presented analyses, and the updated base case and scenario analyses submitted. The Company hopes that the evidence presented and the expected further RWE analyses enable a more informed decision to be made and support access to ^{177}Lu vipivotide tetraxetan for this patient population under routine commissioning.</td><td></td></tr>
<tr><td>2</td><td>Consultee (company)</td><td>Advanced Accelerator Applications</td><td>The ERG’s preferred NMA comparing ^{177}Lu vipivotide tetraxetan and cabazitaxel is inappropriate

The HRs derived from the ERG-preferred NMA are shown below in Table 1, which was based on network including the VISION, CARD and TheraP trials (for rPFS).

Table 1: ERG-preferred rPFS and OS hazard ratios between ^{177}Lu vipivotide tetraxetan and cabazitaxel
<table><tr><th>Scenario</th><th>HR (95% CI)</th></tr><tr><td>^{177}Lu vipivotide tetraxetan vs cabazitaxel (OS)</td><td>[redacted]</td></tr><tr><td>^{177}Lu vipivotide tetraxetan vs cabazitaxel (rPFS)</td><td>[redacted]</td></tr></table>Abbreviations: CI: confidence interval; HR: hazard ratio; OS:</td><td>Thank you for your comment. The committee considered the company’s Bucher indirect treatment comparison and unanchored matching adjusted indirect comparison at the third committee meeting. It concluded that all approaches it had seen to estimate the relative treatment effect between lutetium 177 and cabazitaxel were associated with high uncertainty. This was because all the trials had limitations and because of the heterogeneity between trial populations. Please see FAD section 3.12 for more information.</td></tr>
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			overall survival; rPFS: radiographic progression-free survival. Clinical feedback throughout the submission process has been highly critical of the comparison between CARD and VISION, repeatedly indicating that it produces a biased estimate of the relative treatment effect between ^{177}Lu vipivotide tetraxetan and cabazitaxel. This is because CARD exclusively enrolled patients who had progressed within 12 months of receipt of a prior ARPI, with its results being indicative that ARPI treatment was not effective if used more than once in the treatment pathway. Further clinical feedback has been sought as part of this response which confirms the ERG's preferred analysis based on this comparison is overly pessimistic; clinical experts confirmed that a survival benefit would be expected for ^{177}Lu vipivotide tetraxetan compared with cabazitaxel in clinical practice, and that analyses suggesting no difference in overall survival lack clinical validity.[2] Six clinical experts took part in an elicitation exercise, where they were asked to report their expectations of median overall survival for cabazitaxel used at 3rd line, and what they thought would be the plausible lower and upper bound for this median OS estimate. By comparing their pooled responses (pooled using a linear opinion pooling approach) with that observed in the VISION trial (15.3 months) for ^{177}Lu vipivotide tetraxetan, a distribution for the (log) hazard ratio was obtained.[9] This distribution was assumed to be Normally distributed, and had a mean of -[redacted] and a SD of [redacted], corresponding to a HR of [redacted] and 95% credible intervals (CrI) from [redacted] to [redacted]. Whilst the point estimate of the treatment effect is uncertain, this feedback corroborates the results of analyses presented below, which indicate that ^{177}Lu vipivotide tetraxetan is associated with a survival benefit as compared to cabazitaxel.	

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			The ERG suggest the level of ARPI resistance in the CARD trial and VISION is likely to be similar, but no evidence has been provided to support this assumption; further analysis of the VISION trial (**Error! Reference source not found.**) shows that only ~[redacted]% of patients had reported progression within 12 months of receipt of a prior ARPI, in contrast to all patients enrolled in the CARD trial. The RWE study carried out by Watson *et al.* (2022) cited by the ERG during the second appraisal Committee meeting indicates that response to a prior ARPI has a significant impact on subsequent relative treatment efficacy.[3] Specifically, the treatment effect for patients treated with cabazitaxel was greater, when patients progressed more rapidly, within 12-months of an ARPI, compared to patients who progressed after 12 months of commencing an ARPI, as reflected in the greater relative OS increase. This may partially explain why the treatment effect between ^{177}Lu vipivotide tetraxetan and cabazitaxel expected by clinical experts based on their experience using cabazitaxel in UK patients differs to the results of the EAG-preferred NMA. Accordingly, OS and rPFS are observed to be higher in the ARPI-SOC subgroup of the VISION control arm than the ARPI control arm of CARD (13.5 vs 11.0 months and 3.9 vs 2.7, respectively), despite differences between trials suggesting that patients in VISION should have a poorer prognosis.[4, 10] For example, the VISION trial recruited more heavily pre-treated patients, with close to half of patients (41.1%) having received at least two prior taxanes.[5] Patients in the VISION trial who received ^{177}Lu vipivotide tetraxetan had previously received cabazitaxel (37.9%), further limiting the suitability of performing a comparison between VISION and CARD. Clinical experts confirmed that prognosis is worse for pre-treated patients, and thus these patients would be expected to achieve poorer clinical outcomes than those patients in CARD when receiving similar treatments. Whilst acknowledging the	

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			limitations of a naïve comparison, the poorer survival in the control arm of CARD suggests that the control arms of these trials are not comparable, and that differences between trial populations in the timing of prior ARPI progression are likely to be impacting treatment outcomes. Differences between VISION and CARD in the timing of prior ARPI progression therefore represent important confounders of the relative treatment effect in any indirect comparison, and analyses that fail to resolve these differences are inappropriate. **A Bucher ITC was conducted between the CARD and a subgroup of the VISION trial who met the key eligibility criterion of the CARD trial: patients having progressed *within 12 months of receipt of a prior ARPI*** In order to address the limitations of the ERG and Company NMAs and align with Committee preferences, in particular addressing the heterogeneity in eligibility criteria across the VISION and CARD trials, a subgroup analysis of the VISION trial was explored: • The analysis included the subgroup of patients from the VISION trial who both had ARPI prescribed as part of SOC (the ARPI subgroup, as per the ERG's preferred analysis) but who also met the eligibility criteria for CARD, i.e. those patients *who had progressed within 12 months of receipt of a prior ARPI*, thereby resolving differences between trials in this important treatment effect modifier. • The VISION trial enrolled [redacted] patients having previously progressed within 12 months of receipt of an prior ARPI, [redacted] in the ^{177}Lu vipivotide tetraxetan arm, and [redacted] in	

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the SOC arm, which informed the analysis of OS. rPFS was informed by the corresponding patients in the PFS-FAS analysis set, which included [redacted] patients in the ^{177}Lu vipivotide tetraxetan arm and [redacted] in the SOC arm. Baseline characteristics, rPFS and OS results for this subgroup are presented in full in Error! Reference source not found..

• It should be noted that these subgroups represent a small proportion of all patients enrolled in the VISION trial [redacted] and [redacted] of patients included in the FAS and PFS-FAS, respectively), suggesting a poor overlap between the VISION and CARD trials, and providing further evidence that the ERG's preferred analysis is likely subject to considerable bias in favour of cabazitaxel. These small patient numbers also indicate that this cohort represents a fraction of the real-world population suitable for ^{177}Lu vipivotide tetraxetan, and thus, outcomes resulting from comparisons with CARD apply only to a small proportion of real-world patients.

The HRs for rPFS and OS resulting from a Bucher ITC are presented in Table 2 below.

Table 2: Bucher ITC of OS and rPFS for ^{177}Lu vipivotide tetraxetan (patients who progressed within 12 months of receipt of a prior ARPI) vs cabazitaxel (CARD)

<table>
<tr><th></th><th colspan="2">Bucher ITC</th></tr>
<tr><th></th><th>Hazard Ratio</th><th>95% CrI</th></tr>
<tr><td>^{177}Lu vs cabazitaxel (rPFS)</td><td>[redacted]</td><td>[redacted]</td></tr>
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			[177]Lu vs cabazitaxel (OS) [redacted] [redacted] **Abbreviations:** [177]Lu: [177]Lu vipivotide tetraxetan; CrI: credible interval; OS: overall survival; rPFS: radiographic progression-free survival. The results presented above indicate an OS and rPFS benefit for [177]Lu vipivotide tetraxetan compared to cabazitaxel, and corroborate the expected treatment effect elicited from the clinical experts. This analysis is however associated with some limitations: • Time to progression on an ARPI was not a stratification factor in the VISION trial, therefore the subgroup analysis of the VISION trial focusing on patients who progressed within 12 months of receipt of a prior ARPI breaks randomisation. As shown in **Error! Reference source not found.** in **Error! Reference source not found.**, baseline characteristics were reasonably well-matched across treatment arms, but given the lack of randomisation, observed or unobserved differences in patient characteristics across treatment arms could contribute to differences in observed treatment outcomes, and thereby confound the results of the Bucher ITC. • There are very low patient numbers in the subgroup of the VISION trial who progressed within 12 months of initiation of ARPI treatment, suggesting a poor overlap in patient populations between VISION and CARD, and resulting in wide confidence intervals. Given this subgroup analysis breaks randomisation, adjusting for differences in patient characteristics across the VISION treatment arms was considered, but was not feasible given the already small patient numbers available for	

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			adjustment. • Finally, there is an important distinction between treatment with an ARPI as part of SOC in the VISION trial, and as part of the control arm of CARD. Patients in VISION were prescribed ARPI as part of SOC based on clinical judgement, likely where there may be an expectation of additional clinical benefit. In contrast, patients receiving a second ARPI was mandated in the control arm of CARD,[4] regardless of any anticipated clinical benefit and disease progression within 12 months of treatment with an ARPI, typically associated with rapid ARPI resistance. Indeed, clinical expert feedback during the Committee meeting indicated that the CARD trial demonstrated a lack of clinical benefit associated with *retreatment* with ARPIs, specifically in patients who are likely to have rapidly developed ARPI resistance (within 12 months of treatment with a prior ARPI).[2] This suggests that the control arms of the two trials are heterogeneous in their treatment intentions, and thus the treatment effects derived from each trial are not comparable. Administration of a second ARPI as performed in the CARD trial control arm deviates significantly from NHS clinical and reimbursement practice which limits comparability of the CARD trial control arm with UK clinical practice. Given the numerous limitations, it remains a significant challenge to further reduce uncertainty associated with estimation of comparable relative treatment effects between the interventions of interest (^{177}Lu vipivotide tetraxetan and cabazitaxel) and a second ARPI which form the basis of any anchored ITC. **An unanchored MAIC was performed between the**	

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intervention arms of the CARD and VISION trials, derived from a larger number of patients and adjusting for important differences in patient characteristics between the two trials

In order to provide the Committee with further evidence for relative efficacy between ^{177}Lu vipivotide tetraxetan and cabazitaxel, an alternative indirect comparison of the CARD and VISION trial was conducted. In order to maximise patient numbers available to adjust for differences in variables across the two trials, a unanchored MAIC was carried between the intervention arms of the CARD trial (n=129) and the *ARPI-subgroup population* of the VISION trial (n=243).

The MAIC adjusted for differences in key prognostic factors and treatment effect modifiers between the two studies, as identified via a systematic literature review (SLR) of prognostic variables and confirmed through clinical expert opinion.[2, 8] The variables adjusted for in the MAIC analysis included proportion of patients with ECOG performance status of 0 to 1, presence of liver or lung metastases, presence of bone metastases, proportion of patients who had received docetaxel before ARPI, median age and proportion of patients with Gleason score of 8 to 10. The rPFS and OS HRs (before and after weighting) for ^{177}Lu vipivotide tetraxetan versus cabazitaxel are shown in Table 3. Full details of the methods and results of the MAIC are provided in **Error! Reference source not found.**.

Table 3: rPFS and OS hazard ratios before and after weighing for ^{177}Lu vipivotide tetraxetan versus cabazitaxel (unanchored MAIC between CARD and VISION)

	Before weighting		After weighting	
	Hazard	95% CI	Hazard	95% CI

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	Ratio		Ratio	
^{177}Lu vs cabazitaxel (rPFS)	[redacted]	[redacted]	[redacted]	[redacted]
^{177}Lu vs cabazitaxel (OS)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; MAIC: matching-adjusted indirect comparison; OS: overall survival; rPFS: progression-free survival.

The results of the MAIC corroborate previously presented analyses, with ^{177}Lu vipivotide tetraxetan showing [redacted] survival benefits as compared to cabazitaxel, both for rPFS and OS. Whilst this unanchored comparison remains susceptible to bias from unobserved confounding, this analysis presents various advantages:

- This analysis is based on larger patient numbers, including patients in the intervention arms of CARD and the subpopulation of patients who received ARPI as part of SOC in VISION. This analysis does not adjust for differences in the time to progression on a prior ARPI, but the impact of this effect modifier on outcomes for sequential ARPI no longer biases the estimate of relative effect (the impact of ARPI resistance is likely to have a greater impact on outcomes for sequential ARPI than outcomes for cabazitaxel). Accordingly, whilst highlighting differences in *relative* efficacy, Watson *et al.* (2022) suggests that median OS for cabazitaxel is similar between those who progress within 12 months or prior

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			ARPI initiation and those who progress after 12 months (16.9 months and 17.1, respectively).[3] • Focusing on trial populations is likely to minimise differences in prognosis compared with the propensity score weighting (PSW) analysis presented at Technical Engagement between VISION and the cabazitaxel RWE, and better reporting of characteristics permits more comprehensive adjustment for observed differences in prognostic variables and treatment effect modifiers. Given the greater sample sizes and smaller confidence intervals associated with the unanchored MAIC as compared to the Bucher ITC described above, the MAIC was chosen to inform relative efficacy for OS between ^{177}Lu vipivotide tetraxetan and cabazitaxel in the Company's revised base case analysis. Given the similarity in HRs for rPFS, the HR derived from the ERG-preferred NMA informed relative efficacy for ^{177}Lu vipivotide tetraxetan versus cabazitaxel for rPFS in the revised base case, but the HR for rPFS from the unanchored MAIC was explored in a scenario. The updated base case analysis results are shown in **Error! Reference source not found.** below.	
3	Consultee (company)	Advanced Accelerator Applications	**In line with the Committee's preference, the RWE OS data informs the absolute efficacy of cabazitaxel in the model, with a HR derived from the anchored MAIC used to estimate survival for ^{177}Lu vipivotide tetraxetan** Following ACM2, the Committee reiterated its preference for using the RWE data to estimate absolute OS for cabazitaxel, with a HR derived from the NMA to estimate relative efficacy of	Thank you for your comment. The committee appreciated the company's use of the real-world evidence in its revised base case and noted it was useful to consider. But it had concerns over the company's unanchored matching adjusted indirect comparison. Please see FAD section 3.15 for more information.

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			^{177}Lu vipivotide tetraxetan. The Company note that the VISION trial represents the most reliable source for estimating survival for ^{177}Lu vipivotide tetraxetan in the model. As per the Company response to the first ACD, the parametric model selected for extrapolating ^{177}Lu vipivotide tetraxetan OS (Stratified flexible Weibull [2 knots]) was closely aligned to clinical expert predictions of OS for patients receiving ^{177}Lu vipivotide tetraxetan in UK clinical practice, who estimated survival to be between 9–16% at three years, and 4–8% at four years for ^{177}Lu vipivotide tetraxetan; the Stratified flexible Weibull (2 knots) model predicts [redacted]% and [redacted]% survival for ^{177}Lu vipivotide tetraxetan at three and four years, respectively.[11] However, in order to align with the Committee's preferred analysis, the Company's revised base case uses the cabazitaxel RWE OS data to inform absolute efficacy of cabazitaxel in the model. As outlined in the response to Key Issue 1 above, the unanchored MAIC provides a more reliable estimate of relative efficacy between ^{177}Lu vipivotide tetraxetan and cabazitaxel. As aforementioned, the re-analysis of RWE PSW is underway which is anticipated to provide further evidence for relative efficacy. The HR derived from the unanchored MAIC analysis has therefore been applied to the cabazitaxel RWE OS curve, in order to estimate relative OS efficacy of ^{177}Lu vipivotide tetraxetan in the model. This analysis results in an incremental life-year gain of a [redacted] between ^{177}Lu vipivotide tetraxetan and cabazitaxel, which is substantially greater than the 3-month life extension required to meet NICE's end-of-life criteria. The Company's revised	

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			base case cost-effectiveness estimates are presented in **Error! Reference source not found.**, and clearly demonstrates ^{177}Lu vipivotide tetraxetan to be a cost-effective use of NHS resources at a WTP threshold of £50,000 for end-of-life medicines. For completeness, in order to provide the Committee with results of it's preferred analyses at the second ACM, a scenario analysis has been presented in which both OS and rPFS are based on the ERG-preferred NMA, the results of which can be found in Table 1, **Error! Reference source not found.**. The Company reiterates that this scenario assumes no difference in OS between treatments, and therefore lacks clinical validity. The results should therefore be interpreted with a high degree of caution.	
4	Consultee (company)	Advanced Accelerator Applications	**The Company maintain that a robust comparison of the cost-effectiveness of ^{177}Lu vipivotide tetraxetan versus radium-223 is not feasible. Furthermore, the two treatments are likely to be considered in different patient populations, with radum-223 representing a potential comparator in a small number of patients. The Company have therefore not included radium-223 as a comparator in its revised economic analysis** As noted throughout the submission process, radium-223 is not considered a relevant comparator in this appraisal for the following reasons: • Strict eligibility criteria for the presence of bone metastases and absence of visceral metastases mean that the overlap in patient populations eligible for both ^{177}Lu vipivotide tetraxetan and radium-223 is likely to	Thank you for your comment. The committee concluded that radium-223 dichloride is a relevant comparator for some people, but noted that it had not seen comparative evidence for this group. So, it concluded that it could not make any decision on the comparison of lutetium-177 with radium-223 dichloride for people with symptomatic bone metastases and no known visceral metastases. Please see FAD section 3.5 for more information.

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			be small. As more sensitive PSMA-imaging becomes more widely used in clinical practice, and more visceral metastases are identified, the number of patients eligible for both radium-223 and ^{177}Lu vipivotide tetraxetan is likely to become smaller still. • Clinical feedback received as part of ACD2 response noted that whilst some patients unfit for 3rd-line cabazitaxel may receive radium-223, only a small number of patients do so post-docetaxel and post-ARPI. This is confirmed by RWE data, indicating that only [redacted]% of patients with mCRPC having received prior docetaxel and ARPI (n=[redacted]) went on to receive radium-223 (n=[redacted]). • The clinical lead for the Cancer Drugs Fund noted that, in England, around 700 people start radium-223 each year compared with around 1,000 people starting cabazitaxel. However, [redacted] of patients who were recorded to have received radium-223 in the RWE dataset did so following treatment with prior docetaxel and ARPI, suggesting that the use of radium-223 in clinical practice is not fully aligned with the positioning of ^{177}Lu vipivotide tetraxetan. Further to the small overlap in patient populations between ^{177}Lu vipivotide tetraxetan and radium-223, a robust comparison in the population of interest is not feasible. Heterogeneity between the CARD and ALSYMPCA trials, notably that the ALSYMPCA trial only enrolled ARPI-naïve patients, means that a robust estimate of the relative treatment effect for OS between radium-223 and ^{177}Lu vipivotide	

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			tetraxetan cannot be derived. In addition, the ALSYMPCA trial did not report rPFS, so no comparison for this outcome can be performed. Accordingly, a comparison versus radium-223 was not considered feasible in the recent NICE appraisal of olaparib in a similar indication (adults with hormone-relapsed metastatic prostate cancer with BRCA1 or BRCA2 mutations that has progressed after an ARPI), and thus the exclusion of radium-223 as a comparator was considered acceptable by the ERG.[12] The Company have been unable to source alternative data to inform a robust comparison to radium-223 and ^{177}Lu vipivotide tetraxetan is unlikely to be used in a comparable population. The Company therefore maintain that radium-223 cannot be included as a comparator in this submission, and that its exclusion does not represent a major source of uncertainty.	
5	Consultee (company)	Advanced Accelerator Applications	**The base case analysis is generalisable to patients medically unsuitable for taxanes** Patients medically unsuitable for taxanes face limited treatment options, and therefore the introduction of ^{177}Lu vipivotide tetraxetan would address the high unmet need for a new, innovative and well-tolerated treatment in this population. Clinician feedback has repeatedly confirmed that ^{177}Lu vipivotide tetraxetan is anticipated to be equally efficacious in this patient population as it is in patients previously treated with taxanes. The Committee notes clinical feedback that prognosis in patients medically unsuitable for taxanes may be poorer than in those patients able to receive taxane-based chemotherapy. However, as per the Company responses throughout the post-	Thank you for your comment. The committee was concerned that the company's scenario analyses which assumed that people 'medically unsuitable' for taxanes have a better prognosis than the wider population contradicted clinical expert opinion that the prognosis was likely to be worse. It also understood the evidence informing the better prognosis assumption may not be reflective of the population 'medically unsuitable' for taxanes. It recalled it had not seen scenario analyses that explored a worse prognosis in people who are medically unsuitable for taxanes. The committee acknowledged the high unmet need in people who were medically unsuitable for taxanes. It concluded that

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			submission process, the current poor prognosis for patients not medically suitable for taxanes is a result of the lack of effective treatment options, and therefore may not be a good predictor of the ability of such patients to respond to treatment with ^{177}Lu vipivotide tetraxetan. Many factors informing suitability for taxanes relate to the risks associated with taxane treatment, given their substantial toxicity, and not the ability of the patient to respond to treatment. Furthermore, the patient population of interest (beyond those medically unsuitable for taxanes) is for patients having received *and subsequently progressed* on a taxane. Failure of prior taxane therapy is an important prognostic factor, and thus patients medically unsuitable for taxanes may in fact have an *improved* comparative prognosis on ^{177}Lu vipivotide tetraxetan than patients who have received and failed treatment with docetaxel. This is corroborated by literature evidence identified by the Company: a retrospective study published by Ahmadzadehfar *et al.* (2021) investigated the prognostic impact of prior therapies in patients receiving ^{177}Lu vipivotide tetraxetan and showed that patients who had received prior chemotherapy had poorer survival outcomes than patients who had not.[13] It also showed that there was no difference in OS between patients who had not received chemotherapy and patients for whom chemotherapy was contraindicated.[13] Studies published by Khreish *et al.* (2022) and Barber *et al*. (2019) also support better outcomes for patients receiving ^{177}Lu vipivotide tetraxetan in patients who have not previously received taxanes,[14, 15] as does a recent systematic literature review and NMA published by Satapathy *et al.* (2023).[16]	it was appropriate to consider the whole population included in lutetium 177's marketing authorisation, including when taxanes are 'medically unsuitable'. This is because a proportion of people for whom taxanes are 'medically unsuitable' would be able to have lutetium 177. But it noted that any conclusions made for this population would be subject to substantial uncertainty. Please see FAD section 3.6 for more information.

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			In order to explore the uncertainty in the prognosis of this patient population, the Company has explored additional scenario analyses for the comparison of ^{177}Lu vipivotide tetraxetan versus SOC. In line with the evidence from the literature, a decreased hazard of progression and death was applied to rPFS and OS, respectively, to reflect a better prognosis in the ^{177}Lu vipivotide tetraxetan and SOC arms. The hazard explored in this scenario was informed by the hazard ratio reported in the Ahmadzadehfar *et al.* (2021) study between the subgroups having received prior taxane therapy and those having no prior history of taxane-based chemotherapy. Weighted HRs were calculated from the results of univariate and multivariate analyses performed in Ahmadzadehfar *et al.* (2021) to more closely reflect the patient population in the VISION trial (based on the proportions of patients in VISION with 1 or 2 prior taxanes). Both the weighted HRs resulting from the univariate (HR = 0.649) and multivariate (HR = 0.673) analyses were applied in separate analyses. Ahmadzadehfar *et al.* (2021) was chosen to inform this analysis given its larger sample size compared with other studies identified. The resulting cost-effectiveness estimates for ^{177}Lu vipivotide tetraxetan versus SOC are presented in **Error! Reference source not found.**, and show ^{177}Lu vipivotide tetraxetan to have improved cost-effectiveness versus SOC when better prognosis is modelled. The Company acknowledges limitations in using evidence from a patient population who have not received prior taxane-based chemotherapy as a proxy for a patient population unsuitable for taxanes and thus an assumption of no difference in efficacy is maintained in the base case analysis. However, as indicated by clinical	

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			feedback, medical unsuitability is highly heterogenous, and a significant number of patients would be unsuitable due to personal choice, rather than their medical profile; evidence from pre-taxane patient populations is likely to be generalisable to this patient population. Furthermore, evidence suggests that no difference in OS for ^{177}Lu vipivotide tetraxetan would be expected between patients who have not received chemotherapy and patients for whom chemotherapy is contraindicated (e.g. patients with substantial comorbidities).[13] Therefore, the results of these scenarios are relevant and have been presented in **Error! Reference source not found.** for the Committee's consideration.	
6	Consultee (company)	Advanced Accelerator Applications	**Additional scenarios exploring revised cabazitaxel adverse event (AE) incidence and duration support the use of treatment-dependent utility values** Patient and clinical experts present during ACM2 noted that persistent grade 2 adverse events associated with chemotherapy can have debilitating effects on patients. Advisors highlighted that one such AE is fatigue; the patient expert explained that it took them 12 to 18 months to fully recover from fatigue experienced following treatment with prior taxane-based chemotherapy, whilst they only experienced fatigue for a week following treatment with ^{177}Lu vipivotide tetraxetan. Grade 2 neuropathy was also noted as a persistent issue associated with chemotherapy heavily impacting patients' QoL. The Committee acknowledged this, and noted its preference to consider scenarios using treatment-independent utility values where the impact of these grade 2 adverse events was included. The Company originally only included disutilities associated with grade ≥3 AEs in scenario analyses where treatment-independent utility values were used. Treatment-independent utility values	Thank you for your comment. The committee recalled the high psychological burden that can be associated with best supportive care and cabazitaxel treatment, as described by the clinical and patient experts. The committee preferred to have treatment-independent utilities with adverse event decrements including grade 2 adverse events. It found it helpful to consider the company's scenario analyses exploring treatment-independent utilities and adverse event utility decrements with revised assumptions regarding adverse events for fatigue and neuropathy. It also accepted that using treatment-dependent utility values for decision making may be appropriate in this appraisal but it had not seen any further evidence on the extent and duration of the additional burden associated with treatment with cabazitaxel. Please see FAD section 3.17 for more information.

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			were not used in the base case because this approach is unlikely to fully account for patients' experience of treatment, in particular with cabazitaxel. The Company has conducted three additional scenario analyses using treatment-independent utility values and AE utility decrements with revised assumptions regarding AEs for fatigue and neuropathy: • Treatment-independent utility values were applied and only grade ≥3 AEs were included for ^{177}Lu vipivotide tetraxetan and cabazitaxel (as per original treatment-independent utility scenarios). The duration of disutility for fatigue and neuropathy AEs for cabazitaxel was aligned with treatment duration from CARD (5.06 months), in line with clinical and patient feedback.[17] • Treatment-independent utility values were applied and all-grade neuropathy and fatigue/asthenia AEs were included for ^{177}Lu vipivotide tetraxetan and cabazitaxel. The same utility decrement was applied regardless of grade (in the absence of a reported disutility for grade 1–2 AEs), and no change in AE duration was modelled (i.e. a duration of 1 month modelled for both interventions). • Treatment-independent utility values were applied and all-grade neuropathy and fatigue/asthenia AEs were included for ^{177}Lu vipivotide tetraxetan and cabazitaxel. The same utility decrement was applied regardless of grade (in the absence of a reported disutility for grade 1–2 AEs), and the duration of disutility for these AEs for cabazitaxel was aligned with treatment duration reported in CARD, in line with clinical and patient feedback[17] Incidence of grade 2 AEs were not reported separately in the CARD and VISION trials, and thus all-grade fatigue and	

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neuropathy were used in the final two scenarios (Table 4). A disutility for grade 1–2 AEs could not be sourced, and thus the same utility decrements for all-grade AEs were assumed (Table 5); this is unlikely to hold true in practice, but these scenarios still demonstrate the sensitivity of the cost-effectiveness results to assumptions around the persistence of these low-grade AEs.

Table 4: AE incidence rates explored in scenarios

AE	*Cabazitaxel*		^{177}Lu vipivotide tetraxetan	
	Any grade	*Grade ≥3*	*Any grade*	*Grade ≥3*
Asthenia	*53.2%*	*4.0%*	*6.4%*	[redacted]
Fatigue			*43.1%*	*5.9%*
Peripheral neuropathy	*19.8%*	*3.2%*	[redacted]%[a]	[redacted]%[a]

[a]Includes peripheral sensory, peripheral motor, peripheral sensorimotor, neuropathy peripheral.

Abbreviations: AE: adverse event

Source: Advanced Accelerator Applications Data on File (VISION).[18] de Wit *et al* (2019).[4]

Table 5: Utility decrements associated with AEs explored in scenarios

AE	Disutility	*Source*
Asthenia or fatigue	0.12	Lloyd et al. (2006)[19]
Peripheral neuropathy	*0.145*	*NICE TA259* (2012)[20]

Abbreviations: AE: adverse event; NICE: National Institute of Health and Care Excellence.

The cost-effectiveness results for these scenarios are

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			presented in **Error! Reference source not found.** in **Error! Reference source not found.**. Modelling these persistent AEs noted during ACM2 produces results consistent with the Company's base case analysis using treatment-dependent utility values to account for differences in QoL experienced by patients receiving different treatments. This provides reassurance that the treatment-dependent approach to utility values is a valid and robust method of estimating differences in QoL in the model. Whilst these updated treatment-independent utility scenarios are more representative than those previously presented at technical engagement and preferred by the ERG, the Company maintain that this approach cannot account for all important differences in QoL between treatments. In particular, the psychological burden of receiving further cytotoxic taxane-based chemotherapy or receiving inactive treatment, associated with cabazitaxel and SOC respectively, are important factors not captured in these analyses. The Company therefore maintain that treatment-dependent utility values are most appropriate, and have therefore been retained in the Company's base case economic analysis.	
7	Consultee (company)	Advanced Accelerator Applications	**The costs of PSMA testing accounted for in the model have been aligned to the Committee's preference, following clinical feedback received at ACM2** Feedback from the clinical lead for the Cancer Drugs Fund received as part of ACD2 indicated that accounting for 50–75% of patients in ^{177}Lu vipivotide tetraxetan arm incurring additional costs associated with PSMA testing was most reflective of variation in access to routine testing across England and Wales. The Committee agreed with this estimate. In order to align with the Committee's preference, the Company has updated its base case economic analysis, in which 62.5% of patients in ^{177}Lu vipivotide tetraxetan arm are	Thank you for your comment. At the third committee meeting, the EAG and the committee agreed that including costs for receiving a PET-CT or SPECT scan as part of PSMA testing for 62.5% of patients receiving lutetium 177 was appropriate. Please see FAD section 3.18 for more information.

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			modelled as incurring PSMA testing costs, the midpoint between the Committee's preferred lower and upper estimates (50% and 75%, respectively). The Committee's upper and lower estimates have been explored in scenario analyses presented in **Error! Reference source not found.**. Varying the proportion of patients incurring PSMA testing costs in the ^{177}Lu vipivotide tetraxetan arm in the model has minimal impact on cost-effectiveness estimates, with all results showing ^{177}Lu vipivotide tetraxetan to be a cost-effective treatment option for the NHS at a WTP threshold of £50,000.	
8	Consultee (company)	Advanced Accelerator Applications	**References** 1. Fizazi K, Herrmann K, Krause BJ, et al. Health-related quality of life and pain outcomes with [177Lu]Lu-PSMA-617 plus standard of care versus standard of care in patients with metastatic castration-resistant prostate cancer (VISION): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncology. 2023;24:597 - 610. 2. Advanced Accelerator Applications. Data on File. February 2023 Clinical Expert Advisory Board., 2023. 3. Watson AS, Gagnon R, Batuyong E, et al. Real-World Cabazitaxel Use and Outcomes in Metastatic Castrate-Resistant Prostate Cancer: The Impact of Response to First ARPI. Clin Genitourin Cancer 2022;20:496.e1-496.e9. 4. de Wit R, de Bono J, Sternberg CN, et al. Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. N Engl J Med 2019;381:2506-2518. 5. Sartor O, de Bono J, Chi KN, et al. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. N Engl J Med 2021. 6. National Institute for Health and Care Excellence. Lu vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]. Appraisal consultation	Comment noted. No action required.

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			document. Available at www.nice.org.uk/guidance/gid-ta10730/documents/129. [Last accessed 31/05/2023]. 7. National Institute for Health and Care Excellence. NICE real-world evidence framework. Corporate document [ECD9]. Available at https://www.nice.org.uk/corporate/ecd9/chapter/overview/ [Last accessed 02/06/2023], 2022. 8. Advanced Accelerator Applications. Prognostic factors for survival among patients with metastatic castration-resistant prostate cancer: A systematic literature review., 2023. 9. Stone M. The Opinion Pool. The Annals of Mathematical Statistics 1961;32:1339-1342, 4. 10. Vaishampayan N, Morris MJ, Krause BJ, et al. [177Lu]Lu-PSMA-617 in PSMA-positive metastatic castration-resistant prostate cancer: Prior and concomitant treatment subgroup analyses of the VISION trial. Journal of Clinical Oncology 2022;40:5001-5001. 11. Advanced Accelerator Applications. Data on File. Clinical Expert Validation Interviews., 2022. 12. National Institute for Health and Care Excellence. Olaparib for previously treated BRCA mutation-positive hormone-relapsed metastatic prostate cancer. Technology appraisal guidance [TA887]. Final appraisal determination document. Available at https://www.nice.org.uk/guidance/ta887/documents/final-appraisal-determination-document. [Last accessed 31/05/2023]. 13. Ahmadzadehfar H, Rahbar K, Baum RP, et al. Prior therapies as prognostic factors of overall survival in metastatic castration-resistant prostate cancer patients treated with [(177)Lu]Lu-PSMA-617. A WARMTH multicenter study (the 617 trial). Eur J Nucl Med Mol Imaging 2021;48:113-122.	

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			14. Barber TW, Singh A, Kulkarni HR, et al. Clinical Outcomes of (177)Lu-PSMA Radioligand Therapy in Earlier and Later Phases of Metastatic Castration-Resistant Prostate Cancer Grouped by Previous Taxane Chemotherapy. J Nucl Med 2019;60:955-962. 15. Khreish F, Ghazal Z, Marlowe RJ, et al. 177 Lu-PSMA-617 radioligand therapy of metastatic castration-resistant prostate cancer: Initial 254-patient results from a prospective registry (REALITY Study). Eur J Nucl Med Mol Imaging 2022;49:1075-1085. 16. Satapathy S, Sahoo RK, Bal C. [(177)Lu]Lu-PSMA-Radioligand Therapy Efficacy Outcomes in Taxane-Naïve Versus Taxane-Treated Patients with Metastatic Castration-Resistant Prostate Cancer: A Systematic Review and Metaanalysis. J Nucl Med 2023. 17. National Institute for Health and Care Excellence. Lu vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]. Appraisal consultation document 2. Available at www.nice.org.uk/guidance/gid-ta10730/documents/129-2. [Last accessed 31/05/2023], 2023. 18. Advanced Accelerator Applications. Data on File. Clinical Study Report: VISION, 2021. 19. Lloyd A, Nafees B, Narewska J, et al. Health state utilities for metastatic breast cancer. Br J Cancer 2006;95:683-90. 20. National Institute for Health and Care Excellence. Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen. Technology appraisal guidance [TA259]. Available at: https://www.nice.org.uk/guidance/TA259. [Last accessed: July 2021]. 21. National Institute for Health and Care Excellence DSU.	

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			NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE. 2016. Available at https://www.sheffield.ac.uk/nice-dsu/tsds/population-adjusted. [Last accessed 31/05/2023].	
9	Consultee (professional groups)	Royal College of Physicians (RCP)	The RCP would like to endorse the BNMS response	Comment noted. No action required.
10	Consultee (professional groups)	British Nuclear Medicine Society (BNMS)	• **Has all of the relevant evidence been taken into account?** The BNMS believes that there is no single direct comparator for this innovative treatment appraisal. In the absence of adequately powered direct comparisons of ^{177}Lu vipivotide tetraxetan versus other treatments for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies, any cost-effectives analysis based on the indirect comparison (e.g., Cabazitaxel) would be biased and has important limitations that preclude drawing conclusions regarding the comparative efficacy of ^{177}Lu vipivotide tetraxetan versus Cabazitaxel. Not all evidence has been taken into account. The RWE from Cabazitaxel NHS data base should be included. In addition, CARD study which was included did not reflect current NHS practice and therefore should not be featured in the appraisal. It is not permitted and not cost effective (as previously appraised by NICE) to swich a patient to a second ARPI after a patient has progressed on a previous ARPI. A proportion of patients will develop ARPI resistance within a year and hence this may well overestimate the treatment effect of Cabazitaxel.	Thank you for your comment. The committee concluded that all approaches it had seen to estimate the relative treatment effect between lutetium 177 and cabazitaxel were associated with high uncertainty. This was because all the trials had limitations and because of the heterogeneity between trial populations. Please see FAD section 3.12 for more information.
11	Consultee	British	• **Are the summaries of clinical and cost**	Thank you for your comment. The

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	(professional groups)	Nuclear Medicine Society (BNMS)	**effectiveness reasonable interpretations of the evidence?** The appraisal recognised the novel value of ^{177}Lu vipivotide tetraxetan in treatment of patients with mCRPC, however it has underestimated a major overall importance of this breakthrough radio molecular targeted radiotherapy in cancer treatment. The BNMS therefore urgers NICE to further negotiate the cost to find a way to implement this new game changing treatment in routine clinical NHS practice. We also recognise that the quoted list price is not a real price. We are concerned that there have been some issues with methodology of the assessment (as above). However, we also recognise this has been exceptionally difficult task in absence of any real direct comparator.	committee concluded that there is an unmet need for effective treatment options for PSMA-positive hormone-relapsed metastatic prostate cancer that improve quality of life and survival, and have few side effects. Please see FAD section 3.1 for more information. The Committee understood that the cost effectiveness estimates included a commercial arrangement which had been agreed with NHS England. See section 2.3 of the FAD. The committee considered that all of the cost-effectiveness estimates for lutetium 177 compared with standard care and cabazitaxel that had been presented by both the company and the ERG were considerably above the level that NICE normally considers an acceptable use of NHS resources. So, it concluded that it could not recommend lutetium 177 for treating PSMA-positive hormone-relapsed metastatic prostate cancer.
12	Consultee (professional groups)	British Nuclear Medicine Society (BNMS)	• **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** No. provisional recommendations are not a suitable basis for guidance to the NHS. There is a clear need for additional lines of therapy that can preserve and improve quality of life and provide meaningful survival benefits for patient with mCRPC, which 177Lu-PSMA ^{177}Lu vipivotide tetraxetan treatment can provide.	Thank you for your comment. The committee concluded that there is an unmet need for effective treatment options for PSMA-positive hormone-relapsed metastatic prostate cancer that improve quality of life and survival, and have few side effects. Please see FAD section 3.1 for more information. The committee considered that, once confidential discounts on comparators and postprogression treatments were included, all the cost-effectiveness

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			BNMS is concerned that if this innovative targeted cancer treatment is not accepted for NHS patients it would remain available to those who are insured and can afford it creating a two-tear system and inequalities. Furthermore, there is unmet need for this treatment for patients who are presenting with asymptomatic bone metastases only, lymph node metastases, visceral metastases or both or all, symptomatic bone metastases with lymph node and/or visceral disease, and already undergone and/or cannot tolerate chemotherapy. The provisional recommendation not to recommend ^{177}Lu vipivotide tetraxetan would have a determinantal effect on current and further developments of molecular radiotherapy in England. This treatment has been approved in almost all developed countries and even already widely available in many developing nations (e.g.,South Africa, India etc). Due to a long-term underinvestment, nuclear medicine infrastructure in the UK would require investment and this treatment would need to be gradually adopted indeed. However, this decision would prevent any further developments, leaving England to remain placed within very few last countries in the World to approve this game changing cancer therapy. There is likely to be considerable cost saving too, as this treatment may result into less Cabazitaxel chemotherapy treatments, less hospitalisations, less severe side effects and better quality of life for patients. This preliminary recommendation, if approved, may have a broader implication preventing potential future cancer research for other tumour types (e.g., breast	estimates for lutetium 177 compared with standard care and cabazitaxel from the company and the ERG were considerably above what NICE normally considers an acceptable use of NHS resources. So, it concluded that it could not recommend lutetium 177 for treating PSMA-positive hormone-relapsed metastatic prostate cancer.

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			cancer, brain tumours/high grade glioblastomas, salivary gland tumours etc) in the UK, while most of the World continues with a progress in this field.	
13	Consultee (professional groups)	British Nuclear Medicine Society (BNMS)	**NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.** NHS patients with mCRPC, where cancer has spread despite multiple treatments with high unmet need for new targeted treatment options to improve their outcomes, would be discriminated. They would not have any access to this treatment, while a few centres currently providing PSMA treatment privately would continue to provide it to those who can afford it, creating a two-tear system. We are also concerned that 2nd Committee (ACM2) meeting have been significantly delayed and therefore, clinical experts were not present during the entire meeting due to their prior clinical commitments and could not fully contribute to all discussions. Patients' voices have been very strong in support of PSMA treatment. Their experience with PSMA treatment particularly comparison with side effects and quality of life and outcomes clearly favouring PSMA treatment over chemotherapy should certainly be taken into account.	Thank you for your comment. In accordance with NICE's social value judgement principles, no priority is given based on individuals' income, social class, position in life or social roles in guidance developed for the NHS. NICE's standard approach to economic modelling (the 'reference case') does not compare NHS healthcare with privately funded healthcare. The views of clinical experts and patient representatives were considered by the Appraisal Committee when formulating its recommendations. Please see the FAD for more information.
14	Consultee (professional groups)	British Nuclear Medicine Society (BNMS)	There are some inaccuracies (misinterpretation of discussion with clinical experts) in the consultation document e.g., pg 7. It should read; PSMA-ligands labelled with 68Ga and 18F are available for diagnostic purposes using PET-CT. Choline is completely different and inferior tracer to PSMA (can be labelled with 18F or 11C). It was initially used in the assessment of biochemical recurrence of prostate cancer, before PSMA-ligands were produced, but nowadays choline is only used if PSMA is not available. So, choline is not an isotope (as misrepresented in the document) than a radiotracer inferior to PSMA ligands.	Thank you for your comment. For simplicity, the FAD has been updated to remove the detail on the components used in PET-CT scans.

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15	Consultee (professional groups)	British Nuclear Medicine Society (BNMS)	We would also like to reiterate that 223Radium and 177Lu PSMA (^{177}Lu vipivotide tetraxetan) are entirely different in their mechanisms and hence used for different indications too. In VISION, 17.4% (145/831) of patients received prior treatment with radium-223 and 2.5% of patients received 223Ra following 177Lu-PSMA therapy. Patients with visceral disease (40-50%) are not eligible for 223Radium. Patients with nodal disease (> 3cm) are also not eligible for 223Ra. Patients with nodal disease cannot be treated with 223Ra (bone seeking agent) and patient with PSMA positive nodal disease should be treated with 177LuPSMA. Therefore, there is only a smaller proportion of patient which can potentially be treated with both (symptomatic concordant bone metastasis only). But these patients should be selected for either 223Ra or 177PSMA based on dual tracer diagnostic imaging (18F-NAF/or 99mTc bone scan and PET/SPECT-CT PSMA). There will be some proportion of patients with concordant bone lesions on both scans. However, in the context of high unmet need elsewhere this has a little impact on a broader picture of this overall NICE appraisal. There is evolving evidence that 223Ra and 177Lu-PSMA can be sequentially used with benefit in OS. In a large retrospective study, radium-223 prior 177Lu-PSMA treatment had a positive impact on OS and effect was significant in 2 subgroups: 1. 6-20 bone metastases: OS 16.4 vs 12.1; HR 1.58 (95% CI, 1.0-2.4), *P*=0.038; 2. diffuse bone involvement: OS 11.0 vs 7.1; HR 1.39 (95% CI, 1.0-1.9), *P*=0.034. WARMTH study- Ahmadzadehfar H, et al. *Eur J Nucl Med Mol Imaging*. 2021;48(12):4067-4076. Clinical data from more than 300 patients in retrospective studies suggest that sequential use of radium-223 followed by ^{177}Lu-PSMA-617 is efficacious, without any observed safety signals such as an increased risk for hematotoxicity. *Sartor O, et al. J Nucl Med. 2021;121.262240.*	Thank you for your comment. The committee concluded that radium 223 dichloride is a relevant comparator for some people, but noted that it had not seen comparative evidence for this group. So, it concluded that it could not make any decision on the comparison of lutetium 177 with radium 223 dichloride for people with symptomatic bone metastases and no known visceral metastases. Please see FAD section 3.5 for more information.

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			Ahmadzadehfar H, et al. Oncotarget. 2017;8(33):55567-55574. *Baumgarten J, et al. Cancers. 2022; 14(3):557.* *Groener D, et al. EJNMMI Res. 2021;11(1):61.* In summary, 223Ra should not be a comparator.	
16	Consultee (professional groups)	British Uro-oncology Group (BUG)	This recommendation clearly denies deserving patients the option of treatment with Lutetium-177 vipivotide tetraxetan, within its marketing authorisation.	Thank you for your comment. The committee considered that, once confidential discounts on comparators and postprogression treatments were included, all the cost-effectiveness estimates for lutetium 177 compared with standard care and cabazitaxel from the company and the ERG were considerably above what NICE normally considers an acceptable use of NHS resources. So, it concluded that it could not recommend lutetium 177 for treating PSMA-positive hormone-relapsed metastatic prostate cancer.
17	Consultee (professional groups)	British Uro-oncology Group (BUG)	The proposal from the EAG that Lutetium Lu 177 vipivotide tetraxetan offers no benefit in overall survival versus cabazitaxel is based on a very small number of studies. NICE should consider a different methodology for the CARD study if it feels that the analysis lacks validity. It is not our practice to treat with a second ARPI after relapse on the first ARPI and therefore the control arm in the CARD study is not relevant to our practice. To assess patients progressing on an ARPI within 12 months randomized to another ARPI or cabazitaxel biases any results towards cabazitaxel.	Thank you for your comment. The committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the evidence review group's economic analysis and the companies' submissions. It also carefully considered the comments received from consultees and commentators in response to the evidence review group's report.
18	Consultee (professional groups)	British Uro-oncology Group (BUG)	The British Uro-oncology Group strongly urges NICE to review its ACD to allow appropriate patients the option of this clinically beneficial treatment.	Thank you for your comment. The committee considered that, once confidential discounts on comparators and postprogression treatments were included, all the cost-effectiveness

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				estimates for lutetium 177 compared with standard care and cabazitaxel from the company and the ERG were considerably above what NICE normally considers an acceptable use of NHS resources. So, it concluded that it could not recommend lutetium 177 for treating PSMA-positive hormone-relapsed metastatic prostate cancer.
19	Consultee (patient/carer groups)	Prostate Cancer UK	**We are concerned that this recommendation may imply that real-world evidence is not being considered in the absence of conclusive clinical trial evidence.** We recognise that the current data comparing Lutetium-177 with cabazitaxel is uncertain due to the limitations associated with the TheraP trial and the trials included in the network meta-analysis. We, therefore, urge the committee to consider the real-world evidence submitted by the company to assess the comparison between Lutetium-177 and cabazitaxel under the NICE Real-World Evidence Framework. This is because the framework was supposedly designed so that real-world evidence can be used to resolve gaps in knowledge, improve recommendations and speed up access of patients to new effective interventions such as Lutetium-177 - a novel targeted therapy agent that sets the pace for precision medicine for the treatment of metastatic hormone-relapsed prostate cancer. Moreover, during this appraisal process, several clinical experts have said that the real-world evidence submitted, is more likely to reflect clinical practice as it is more relevant to the population of men who will be receiving the treatment in the UK. Thus, it is essential that rea-world data is not ignored in this process.	Thank you for your comment. The committee agreed that the real-world evidence study was a useful data source, and provided a measure of survival representative of NHS clinical practice. The committee also appreciated the company's use of the real-world evidence in its revised base case and noted it was useful to consider. But it had concerns over the company's unanchored matching adjusted indirect comparison. Please see FAD section 3.15 for more information.

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20	Consultee (patient/carer groups)	Prostate Cancer UK	**We are concerned that this recommendation may also imply that patients' lived experiences are not being considered in the absence of conclusive clinical trial evidence.** Lutetium has been associated with fewer 3+ side effects and an increased quality of life when compared to standard of care. This has been confirmed not only by clinicians but by patient experts too. For example, A patient who is currently receiving Lutetium-177 under the PSMAfore clinical trial described his positive experience with the treatment. To quote, "I am much stronger, and I feel much calmer and more relaxed because I am aware of the next steps and when my cycles are coming up. Also, other than the occasional dry mouth (which my doctor has given me something for), my experience with this treatment has been extraordinary as I don't really experience any other side effects". While another patient treated with Lutetium-177 has said: "As the treatment is targeted, the side-effects are minimal enabling me to continue my work and bike riding. I will be taking part in the stage 2 of the Tour de France."	Thank you for your comment. The views of clinical experts and patient representatives were considered by the Appraisal Committee when formulating its recommendations. Please see FAD section 3.9 for more discussion of patient and clinical experts' experiences of lutetium 177's adverse events.
21	Consultee (patient/carer groups)	Prostate Cancer UK	**This recommendation also suggests that clinicians' expertise is not being taken into account in the absence of conclusive clinical trial evidence.** In the absence of updated survival data, we urge the committee to consider clinicians' expertise, who administer the treatment to men with the condition and have observed the impact of Lutetium-177 in the life expectancy and quality of life	Thank you for your comment. The views of clinical experts were considered by the Appraisal Committee when formulating its recommendations. Please see the FAD for more information.

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			of their patients first hand.	
22	Consultee (patient/carer groups)	Prostate Cancer UK	**We are concerned with this recommendation as there is a need for novel targeted therapies.** We disagree that Lutetium-177 is not innovative beyond what is captured in the cost- effectiveness estimates. Lutetium-177 is the first radioligand treatment of its kind for men with advanced prostate cancer. It sets the pace for precision medicine in prostate cancer and has shown to maintain quality of life and improve survival among patients with an unmet need and limited treatment options. Clinician and patient experts have provided robust evidence of the benefits and innovative aspects of the treatment throughout the appraisal process, and we urge the committee to consider their expertise in the absence of trial data.	Thank you for your comment. The committee acknowledged the innovative aspects of lutetium 177. But it concluded that there were no additional benefits associated with it that had not been captured in the cost-effectiveness estimates. The committee also recognised that there is an unmet need for effective treatment options for PSMA-positive hormone-relapsed metastatic prostate cancer that improve quality of life and survival, and have few side effects. The views of clinical experts were considered by the Appraisal Committee when formulating its recommendations. Please see the FAD for more information.
23	Consultee (patient/carer groups)	Tackle Prostate Cancer	I write as the patient representative for Tackle Prostate Cancer. I was present as one of the patient experts at the recent appraisals for Lutetium 177. [redacted] I received the [redacted] e-mail from NICE stating that [redacted] this would not recommend the use of Lu177 for the treatment of advanced prostate cancer in patients who had already undergone several therapies I have had time to consider this decision. I have also been prompted to write to you having last night talked with a group of men who have advanced prostate cancer. This group meets regularly online as part of Tackle's Peer Support Programme.	Thank you for your comment. Deciding which treatments to recommend involves balancing the needs and wishes of individuals and the groups representing them against those of the wider population. This sometimes means treatments are not recommended because they do not provide sufficient benefit to justify their cost (Social Value Judgements; 'Principles for the development of NICE guidance', principle 2). The Committee considered all the

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			The plight of many of these men who literally have no further treatment currently available to them was obvious. Some of those present would be highly likely to gain benefit from Lu 177 treatment. One man is benefiting from treatment under the EAMS scheme. From my previous experience with NICE, I'm aware that a final decision via the FAD is difficult to overturn and that there are limited reasons for which an appeal against that FAD may be made. Before the FAD is finalised I would like to make the following comments: 1) Neither Tackle nor myself personally have the required scientific or statistical background to comment on all of the discussion that took place. However to a layperson there were obvious differences between the Company and the ERG concerning many of the elements of the appraisal. 2) Similarly, we cannot make valid comments and cost issues or health economics. Indeed we were not admitted to Part B of the committee meeting. However I firmly believe it is not the function of the patient representative to decide what the NHs can or cannot afford - that is for the politicians to sort out. it is my remit 2 ensure the best treatment is made available to all appropriate patients - however many or few the numbers of those patients maybe. 3) The FAD would appear to be directly in opposition to the views expressed by the clinical experts appointed by NICE themselves. The views of the ERG obviously 'preferred' by NICE. All of the clinical experts were of the same opinion - which from my previous experience in the past is unusual where there has not uncommonly been a degree of dissention amongst the clinical experts. Such experts are deemed to be independent of external influences from either the Company	evidence submitted, including evidence from clinical trials, patient and clinical experts, the evidence review group's economic analysis and the companies' submissions. It also carefully considered the comments received from C&Cs in response to the evidence review group's report. The committee did not see cost-effectiveness estimates within the range considered an acceptable use of NHS resources. So, it concluded that it could not recommend lutetium 177 for treating PSMA-positive hormone-relapsed metastatic prostate cancer. The committee also concluded that it could not be considered for use in the Cancer Drugs Fund. In accordance with NICE's social value judgement principles, no priority is given based on individuals' income, social class, position in life or social roles in guidance developed for the NHS. NICE's standard approach to economic modelling (the 'reference case') does not compare NHS healthcare with privately funded healthcare.

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			involved in the appraisal and indeed from NICE themselves. 4) Patients will find it very difficult to understand why a treatment already approved by NICE for a different cancer (neuro-endocrine tumours) is refused approval for the treatment of another cancer. This of course may be on the grounds of lack of clinical evidence of reasonable efficacy in the cancer under discussion. In order to obtain increased clinical experience with a new treatment I believe that there can be a mechanism whereby the treatment under discussion could continue to be used under close observation and data collection until sufficient evidence is available. I believe the Cancer Drugs Fund is sometimes used to provide such a mechanism? However this has already been rejected in the ACD. 5) Lu177 is already approved for treatment of advanced prostate cancer in other countries e.g. USA, Germany, Australia. in addition Lu177 is also available for use in the private sector in the UK. The treatment is obviously considered to be safe and effective. NHS patients will obviously ask why such a treatment cannot be made available to them as well - and indeed that question has already been asked of me when patients have discussed their treatment options with me in my role as providing peer support to them. 6) A further fundamental question asked of me was “if nice do refuse to recommend Lu177 , what happens with the future use of PSMA technology and the mechanism of molecular radiotherapy” It is not uncommon for more than one company to be involved in the same technology. The decision by NICE for Lu177 could potentially influence the progress of the use of this valuable new approach to the treatment of advanced prostate cancer.	

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			I appreciate that decisions made by NICE are often difficult to make. the comments from patients may not always be based on hard fact and clinical research. However as the 'end users' of treatments patients do need their views to be expressed openly. That I believe is my job as a patient representative. I am unsure whether any change or softening of the current decision by NICE is possible I do not know but I felt I should communicate my thoughts to you.	
24	Web comment	Submission 1 - 16	Note: 16 separate submissions were received as part of the web comments. The individual comments have been themed below.	Thank you for your comments. Please see responses to individual issues below.
25	Web comment	Submission 1 – 16	**Theme 1:** unfair variation in access by location: • Unclear why the treatment should be available in other countries but not be available in England. • There is a UK postcode lottery where men can get treatments in Scotland but not in the rest of the UK. This is not fair or equitable. • Need to be acutely mindful of discrimination based upon post-code. Regions of the UK outside of the South East and North west of England significantly lack in availability of diagnostic and therapeutic molecular radiotherapy facilities. There needs be an urgent acknowledgement of this going forward	Thank you for your comments. Issues relating to access to services and implementing guidance in NHS practice cannot be addressed in a technology appraisal.
26	Web comment	Submission 1 - 16	**Theme 2:** Unfair the treatment is available for those who can afford to purchase it privately but not for use in the NHS	Thank you for your comments. In accordance with NICE's social value judgement principles, no priority is given based on individuals' income, social class, position in life or social roles in guidance developed for the NHS. NICE's standard approach to economic modelling (the 'reference case') does not compare NHS healthcare with privately funded healthcare.
27	Web comment	Submission 1 - 16	**Theme 3:** The recommendation is considered to be discriminatory against age and sex because prostate cancer is	Thank you for your comments. Issues related to differences in prevalence or

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			among the more prevalent cancers in men and also one that may be diagnosed late. As a male in his 70's I consider this to be discriminatory against my age and sex.	incidence of a disease cannot be addressed in a technology appraisal.
28	Web comment	Submission 1 – 16	**Theme 4:** Approving this drug will give people: • hope for further treatment options in the future • the chance to live/work/contribute to society/spend time with loved ones for longer • to chance to continue in reasonable health and quality of life	Thank you for your comments. Deciding which treatments to recommend involves balancing the needs and wishes of individuals and the groups representing them against those of the wider population. This sometimes means treatments are not recommended because they do not provide sufficient benefit to justify their cost (Social Value Judgements; 'Principles for the development of NICE guidance', principle 2). The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the evidence review group's economic analysis and the companies' submissions. It also carefully considered the comments received from C&Cs in response to the evidence review group's report. The committee considered that, once confidential discounts on comparators and postprogression treatments were included, all the cost-effectiveness estimates for lutetium 177 compared with standard care and cabazitaxel from the company and the ERG were considerably above what NICE normally considers an acceptable use of NHS

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				resources. So, it concluded that it could not recommend lutetium 177 for treating PSMA-positive hormone-relapsed metastatic prostate cancer.
29	Web comment	Submission 1 - 16	**Theme 5:** NICE should give more consideration to the feelings and views of patients whose lives are directly affected by their decisions.	Thank you for your comments. Deciding which treatments to recommend involves balancing the needs and wishes of individuals and the groups representing them against those of the wider population. This sometimes means treatments are not recommended because they do not provide sufficient benefit to justify their cost (Social Value Judgements; 'Principles for the development of NICE guidance', principle 2). The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the evidence review group's economic analysis and the companies' submissions. It also carefully considered the comments received from C&Cs in response to the evidence review group's report. The committee considered that, once confidential discounts on comparators and postprogression treatments were included, all the cost-effectiveness estimates for lutetium 177 compared with standard care and cabazitaxel from the company and the ERG were considerably above what NICE normally

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				considers an acceptable use of NHS resources. So, it concluded that it could not recommend lutetium 177 for treating PSMA-positive hormone-relapsed metastatic prostate cancer.
30	Web comment	Submission 1 – 16	**Theme 6:** All of the relevant evidence has not been taken into account / been taken into account but not appreciated appropriately • for patients with PSMA-positive mCRPC disease, Pluvicto is a superior treatment to a non-selective/targeted taxane chemotherapy agent. It is our belief that approving the use of Pluvitco will reduce the number of inpatient admissions due to sepsis when compared to Cabazitaxel, which in turn will help reduce the number of A&E admissions, in-patient bed days, etc. and thereby save overall costs • once the UK has invested in the necessary upgrades required for molecular radiotherapy services - both diagnostic and therapeutic - the cost of treatment will be significantly reduced • the TheraP trial clearly demonstrates improvements in patient quality of life versus Cabazitaxel chemotherapy as well as a strong hint on overall survival benefit • treatment is generally well tolerated with some minor treatment related side effects. • current ICER calculations do not take into account the benefits of not giving ineffective treatment. They also do not include costs associated with infrastructure for	Thank you for your comments. The committee concluded that lutetium 177 may be better tolerated than chemotherapy. Please see FAD section 3.9 for more information. The economic model included costs associated with the management of symptomatic skeletal event and adverse events. The committee discussed access to PSMA imaging. Please see FAD section 3.3 for more information. The committee discussed health related quality of life. Please see FAD section 3.16 and section 3.17 for more information. The committee concluded that lutetium 177 may be better tolerated than chemotherapy. Please see FAD section 3.9 for more information. The committee concluded that PSMA imaging is needed to determine eligibility for treatment with lutetium 177. It agreed

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			diagnostics	that, although some people already have PSMA PET-CT scans in the NHS, clinical practice varies and they are not standard for everyone. Please see FAD section 3.3 for more information.
			• This drug needs a chance to be utilised within the real world, only then will the true benefits be realised.	The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the evidence review group's economic analysis and the companies' submissions. It also carefully considered the comments received from C&Cs in response to the evidence review group's report. The committee did not see cost-effectiveness estimates within the range considered an acceptable use of NHS resources. So, it concluded that it could not recommend lutetium 177 for treating PSMA-positive hormone-relapsed metastatic prostate cancer.
31	Web comment	Submission 1 - 16	**Theme 7:** It is a concern that the spc does not satisfy UK regulations regarding patient dosimetry and that this does not seem to have been considered as yet.	Thank you for your comments. Issues relating to access to services and implementing guidance in NHS practice cannot be addressed in a technology appraisal.

NICE National Institute for Health and Care Excellence

^{177}Lu vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]

Consultation on the appraisal consultation document – deadline for comments 5pm on 2nd June 2023 **Return via:** NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: · has all of the relevant evidence been taken into account? · are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? · are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: · could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; · could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Advanced Accelerator Applications**

NICE National Institute for Health and Care Excellence

^{177}Lu vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]

Consultation on the appraisal consultation document – deadline for comments 5pm on 2nd June 2023 **Return via:** NICE DOCS

Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**
Name of commentator person completing form:	[redacted]

Comment number	Comments
Summary	Advanced Accelerator Applications have presented detailed responses to address the Committee's remaining key areas of uncertainty, as well as a revised economic base case and supporting scenario analyses as requested by the Committee. The Committee recognised the considerable unmet need associated with metastatic castration-resistant prostate cancer (mCRPC) in patients having previously received treatment with androgen receptor pathway inhibitors (ARPIs) and taxane-based chemotherapy, or who are medically unsuitable for taxanes. This unmet need is multifaceted, with patients facing a poor prognosis and limited treatment options. Clinical experts further noted during both Appraisal Committee Meetings (ACMs) that the primary treatment option at this stage of disease, cabazitaxel, is associated with debilitating side effects. ^{177}Lu vipivotide tetraxetan represents the first PSMA-targeted radioligand therapy to receive marketing authorisation for the treatment of prostate cancer, offering a targeted approach to treatment able to improve survival benefits with a tolerable safety profile. The Committee heard from patient representatives having received ^{177}Lu vipivotide tetraxetan following receipt of prior taxanes, and the vast improvement in quality of life (QoL) they felt following receipt of ^{177}Lu vipivotide tetraxetan, compared to prior taxane-based therapy.[1] In this response to the second Appraisal Consultation Document (ACD2), the Company has provided detailed responses to address the Committee's key areas of uncertainty surrounding the Company's submission:

	• The suitability of the Company's network meta-analysis (NMA) to inform the relative efficacy of ^{177}Lu vipivotide tetraxetan and the principal comparator, cabazitaxel • The use of real-world evidence (RWE) to estimate relative treatment effects in overall survival (OS) between cabazitaxel and ^{177}Lu vipivotide tetraxetan • A thorough re-analysis of the RWE is being undertaken, in order to further resolve committee uncertainty surrounding the use of RWE data to inform treatment effect in the model • The unavailability of robust data to inform the comparison between ^{177}Lu vipivotide tetraxetan and standard of care (SOC) in the population of patients for whom taxanes are medically unsuitable • The exclusion of radium-223 as a comparator in the Company submission • The Company's estimates of health-state utility values associated with each of the treatments considered in the economic analysis The NICE Committee have stated they have not yet seen their preferred analysis using real-world evidence for OS for cabazitaxel as a reference group for the absolute event estimates, and applying the hazard ratio (HR) for the relative effect on OS between ^{177}Lu vipivotide tetraxetan and cabazitaxel from the ERG-preferred NMA to estimate OS for ^{177}Lu vipivotide tetraxetan. Clinical experts question the plausibility of this approach, as the difference between predicted OS and radiographic progression-free survival (rPFS) for ^{177}Lu vipivotide tetraxetan seem implausible given the mismatch in data sources (rPFS for ^{177}Lu vipivotide tetraxetan is still based on direct trial data from the VISION trial). Fundamentally this approach relies on a biased treatment effect for cabazitaxel informed by the CARD study. CARD results do not reflect UK practice, in which ARPI sequencing is not endorsed by NHS commissioning due to the lack of evidence of clinical benefit of such practice. Furthermore, the CARD trial exclusively enrolled patients who had progressed *within 12 months* on a prior ARPI, which is likely to be a treatment effect modifier. As confirmed by clinical expert feedback, patients who had progressed within 12 months of ARPI treatment were likely to have developed ARPI resistance and would show poor outcomes with receipt of a second ARPI, thereby biasing relative treatment effect towards cabazitaxel.[2] The biased hazard ratio from the ERG-preferred NMA therefore does not reflect the relative treatment effect between ^{177}Lu vipivotide tetraxetan and cabazitaxel that is anticipated in the population who would be eligible for ^{177}Lu vipivotide tetraxetan in UK clinical practice .[2] Seven UK clinical experts gave their opinions during a recent advisory board meeting, experts are unanimous in their opinion that ^{177}Lu vipivotide tetraxetan is predicted to offer patients longer survival than cabazitaxel. Following the first Appraisal Committee Meeting (ACM), the Committee concluded that both the Company and ERG NMAs comparing ^{177}Lu vipivotide tetraxetan with cabazitaxel were associated with high uncertainty due to heterogeneity across the included trials, and that further exploratory analyses were required to resolve uncertainty.

	Following the second ACM, the Committee favoured the ERG's analysis where trials that exclusively enrolled ARPI-naïve patients were excluded, because previous ARPI treatment is likely to be a treatment effect modifier. However, the trials included in the ERG's NMA (VISION, CARD and TheraP) were unchanged between the first and second Committee meetings, and thus these analyses remain subject to high uncertainty and are inappropriate, as outlined later in the response to Key Issue 1 below. The ERG further noted that timing of progression on a prior ARPI may be a treatment effect modifier for response to cabazitaxel, as evidenced by a real-world study conducted by Watson *et al.* (2022).[3] The CARD trial exclusively enrolled patients who had progressed within 12 months of initiating a prior ARPI;[4] patients in the VISION trial had received a prior ARPI, but there were no criteria relating to the duration of response prior to progression. Importantly, only a small proportion (~[redacted]%) of patients in VISION were reported to have progressed within 12 months of initiating a prior ARPI.[5] The ERG and NICE Committee acknowledged that the timing of progression on a prior ARPI is likely a treatment effect modifier, and thus the treatment effects derived from VISION and CARD are not comparable. On this basis, clinical experts strongly disagreed with CARD's inclusion in the NMAs as it is biases the hazard ratio and is not reflective of UK practice.[6] Furthermore, as per the Watson *et al.* (2022) study, only 68.1% of the mCRPC patient population (n=592) had disease progression within 12 months of initiating their first ARPI treatment.[3] As such, the CARD trial fails to account for one-third of the mCRPC patient population and its results are not reflective of real-world clinical practice. In order to present the Committee with the analyses requested, the Company has provided the following analyses: • In line with Committee preferences, the OS estimates for cabazitaxel derived from the RWE study have been used as the reference, to which a hazard ratio (HR) has been applied to derive OS estimates for ^{177}Lu vipivotide tetraxetan, including HRs derived from the ERG-preferred NMA. • In line with Committee preferences, trials that enrolled exclusively ARPI-naïve patients were excluded from the indirect treatment comparisons (ITC) informing relative efficacy between ^{177}Lu vipivotide tetraxetan and cabazitaxel. • ITCs focused on the CARD trial and the subpopulation of patients who received ARPI as part of SOC in both VISION treatment arms, in line with the EAG's preferences. However, given timing of progression on a prior ARPI has been shown to be an important treatment effect modifier for sequential ARPI treatment, the ARPI-SOC arm of VISION and the control arm of CARD do not form a true common comparator, and the results of these ITCs are biased in favour of the cabazitaxel. To reduce heterogeneity and resulting bias in the ITC, the following additional analyses were explored: o A Bucher ITC was conducted between the CARD and a subgroup of the VISION trial who met the eligibility criterion of the CARD trial: patients

	having progressed *within 12 months of receipt of a prior ARPI*, who are likely to have developed rapid ARPI resistance. This approach aims to directly address the heterogeneity between the trials forming the basis of networks proposed by both the Company and EAG, namely VISION and CARD. However, this analysis is limited by breaking of randomisation and small number patient numbers in the VISION subgroup. o Given the remaining limitations associated with the Bucher ITC, it is challenging to estimate comparable relative effects between the interventions of interest (^{177}Lu vipivotide tetraxetan and cabazitaxel) and a second ARPI. Therefore, an unanchored matching adjusted indirect comparison (MAIC) was performed between the intervention arms of the CARD and VISION trials, adjusting for differences in key prognostic variables and treatment effect modifiers. This analysis presents various advantages and has been incorporated in the Company's revised base case. o Further details of the Bucher ITC and unanchored MAIC are provided in the response to Key Issue 1 below, as well as Appendix 3 and Appendix 4. These analyses both offer further evidence for ^{177}Lu vipivotide tetraxetan's superior treatment efficacy over cabazitaxel (see response to Key Issue 1). The Company also reiterates the importance and relevance of the RWE analysis previously presented in the original submission particularly as it addresses the key concerns with using an NMA informed by a trial subject to selection bias and not reflective of UK clinical practice. In line with the principles detailed in the NICE real-world evidence framework,[7] the UK RWE study would provide estimates of relative treatment effects representative of clinical practice. In order to address the committee and EAG's concerns and further improve the reliability of the UK RWE as a source of relative efficacy for ^{177}Lu vipivotide tetraxetan and cabazitaxel in the model, the Company is conducting a re-analysis of the PSW originally performed, selecting patients from the RWE dataset who meet key eligibility criteria from the VISION trial, and aiming to adjust for a greater number of prognostic factors and treatment effect modifiers (as identified from a systematic literature review [SLR] of prognostic factors and confirmed through clinical expert feedback).[8] The results of this re-analysis are unfortunately not yet available for inclusion in the Company response. The Company however expects the results to more closely reflect UK practice, in line with clinical expert opinion and corroborate those of the Bucher ITC and unanchored MAIC detailed in this response, providing the Committee with further evidence of improved survival with ^{177}Lu vipivotide as compared to cabazitaxel. This analysis will be shared with the Committee when available in order to provide all relevant information to make an informed decision on the relative treatment effect. The revised base case and additional scenario analyses presented demonstrate that treatment with ^{177}Lu vipivotide tetraxetan extends life over 3 months. In the revised company base case, median OS is estimated to be [redacted] months for ^{177}Lu vipivotide tetraxetan compared to [redacted] months for cabazitaxel, and incremental life years gained (LYG) are estimated to be

	[redacted], thus ^{177}Lu vipivotide tetraxetan meets the NICE end-of-life criteria. The updated base case is associated with an incremental cost-effectiveness ratio (ICER) versus cabazitaxel below the willingness-to-pay (WTP) threshold of £50,000 for medicines which reach the end-of-life criteria and thus demonstrates ^{177}Lu vipivotide tetraxetan to be a cost-effective use of NHS resources. The Company has additionally explored scenarios to address remaining uncertainty which provide validation for the base case approach. The Company therefore strongly urges the Committee to reconsider the best approach to inform the relative treatment effect, given the issues highlighted in the ITCs previously considered, the results of the newly presented analyses, and the updated base case and scenario analyses submitted. The Company hopes that the evidence presented and the expected further RWE analyses enable a more informed decision to be made and support access to ^{177}Lu vipivotide tetraxetan for this patient population under routine commissioning.
1	**The ERG's preferred NMA comparing ^{177}Lu vipivotide tetraxetan and cabazitaxel is inappropriate** The HRs derived from the ERG-preferred NMA are shown below in Table 1, which was based on network including the VISION, CARD and TheraP trials (for rPFS). **Table 1: ERG-preferred rPFS and OS hazard ratios between ^{177}Lu vipivotide tetraxetan and cabazitaxel** | Scenario | HR (95% CI) | | ^{177}Lu vipivotide tetraxetan vs cabazitaxel (OS) | [redacted] ([redacted], [redacted]) | | ^{177}Lu vipivotide tetraxetan vs cabazitaxel (rPFS) | [redacted] ([redacted], [redacted]) | **Abbreviations:** CI: confidence interval; HR: hazard ratio; OS: overall survival; rPFS: radiographic progression-free survival. Clinical feedback throughout the submission process has been highly critical of the comparison between CARD and VISION, repeatedly indicating that it produces a biased estimate of the relative treatment effect between ^{177}Lu vipivotide tetraxetan and cabazitaxel. This is because CARD exclusively enrolled patients who had progressed within 12 months of receipt of a prior ARPI, with its results being indicative that ARPI treatment was not effective if used more than once in the treatment pathway. Further clinical feedback has been sought as part of this response which confirms the ERG's preferred analysis based on this comparison is overly pessimistic; clinical experts confirmed that a survival benefit would be expected for ^{177}Lu vipivotide tetraxetan compared with cabazitaxel in clinical practice, and that analyses suggesting no difference in overall survival lack clinical validity.[2] Six clinical experts took part in an elicitation exercise, where they were asked to report their expectations of median overall survival for cabazitaxel used at 3rd line, and what they thought would be the plausible lower and upper bound for this median OS estimate. By comparing their pooled

	responses (pooled using a linear opinion pooling approach) with that observed in the VISION trial (15.3 months) for ^{177}Lu vipivotide tetraxetan, a distribution for the (log) hazard ratio was obtained.[9] This distribution was assumed to be Normally distributed, and had a mean of -[redacted] and a SD of [redacted], corresponding to a HR of [redacted] and 95% credible intervals (CrI) from [redacted] to [redacted]. Whilst the point estimate of the treatment effect is uncertain, this feedback corroborates the results of analyses presented below, which indicate that ^{177}Lu vipivotide tetraxetan is associated with a survival benefit as compared to cabazitaxel. The ERG suggest the level of ARPI resistance in the CARD trial and VISION is likely to be similar, but no evidence has been provided to support this assumption; further analysis of the VISION trial (Appendix 3) shows that only ~[redacted]% of patients had reported progression within 12 months of receipt of a prior ARPI, in contrast to all patients enrolled in the CARD trial. The RWE study carried out by Watson *et al.* (2022) cited by the ERG during the second appraisal Committee meeting indicates that response to a prior ARPI has a significant impact on subsequent relative treatment efficacy.[3] Specifically, the treatment effect for patients treated with cabazitaxel was greater, when patients progressed more rapidly, within 12-months of an ARPI, compared to patients who progressed after 12 months of commencing an ARPI, as reflected in the greater relative OS increase. This may partially explain why the treatment effect between ^{177}Lu vipivotide tetraxetan and cabazitaxel expected by clinical experts based on their experience using cabazitaxel in UK patients differs to the results of the EAG-preferred NMA. Accordingly, OS and rPFS are observed to be higher in the ARPI-SOC subgroup of the VISION control arm than the ARPI control arm of CARD (13.5 vs 11.0 months and 3.9 vs 2.7, respectively), despite differences between trials suggesting that patients in VISION should have a poorer prognosis.[4, 10] For example, the VISION trial recruited more heavily pre-treated patients, with close to half of patients (41.1%) having received at least two prior taxanes.[5] Patients in the VISION trial who received ^{177}Lu vipivotide tetraxetan had previously received cabazitaxel (37.9%), further limiting the suitability of performing a comparison between VISION and CARD. Clinical experts confirmed that prognosis is worse for pre-treated patients, and thus these patients would be expected to achieve poorer clinical outcomes than those patients in CARD when receiving similar treatments. Whilst acknowledging the limitations of a naïve comparison, the poorer survival in the control arm of CARD suggests that the control arms of these trials are not comparable, and that differences between trial populations in the timing of prior ARPI progression are likely to be impacting treatment outcomes. Differences between VISION and CARD in the timing of prior ARPI progression therefore represent important confounders of the relative treatment effect in any indirect comparison, and analyses that fail to resolve these differences are inappropriate.

A Bucher ITC was conducted between the CARD and a subgroup of the VISION trial who met the key eligibility criterion of the CARD trial: patients having progressed *within 12 months of receipt of a prior ARPI*

In order to address the limitations of the ERG and Company NMAs and align with Committee preferences, in particular addressing the heterogeneity in eligibility criteria across the VISION and CARD trials, a subgroup analysis of the VISION trial was explored:

- The analysis included the subgroup of patients from the VISION trial who both had ARPI prescribed as part of SOC (the ARPI subgroup, as per the ERG's preferred analysis) but who also met the eligibility criteria for CARD, i.e. those patients *who had progressed within 12 months of receipt of a prior ARPI*, thereby resolving differences between trials in this important treatment effect modifier.
- The VISION trial enrolled [redacted] patients having previously progressed within 12 months of receipt of an prior ARPI, [redacted] in the ^{177}Lu vipivotide tetraxetan arm, and [redacted] in the SOC arm, which informed the analysis of OS. rPFS was informed by the corresponding patients in the PFS-FAS analysis set, which included [redacted] patients in the ^{177}Lu vipivotide tetraxetan arm and [redacted] in the SOC arm. Baseline characteristics, rPFS and OS results for this subgroup are presented in full in Appendix 3.
- It should be noted that these subgroups represent a small proportion of all patients enrolled in the VISION trial ([redacted] and [redacted] of patients included in the FAS and PFS-FAS, respectively), suggesting a poor overlap between the VISION and CARD trials, and providing further evidence that the ERG's preferred analysis is likely subject to considerable bias in favour of cabazitaxel. These small patient numbers also indicate that this cohort represents a fraction of the real-world population suitable for ^{177}Lu vipivotide tetraxetan, and thus, outcomes resulting from comparisons with CARD apply only to a small proportion of real-world patients.

The HRs for rPFS and OS resulting from a Bucher ITC are presented in Table 2 below.

Table 2: Bucher ITC of OS and rPFS for ^{177}Lu vipivotide tetraxetan (patients who progressed within 12 months of receipt of a prior ARPI) vs cabazitaxel (CARD)

	Bucher ITC	
	Hazard Ratio	**95% CrI**
^{177}Lu vs cabazitaxel (rPFS)	[redacted]	[redacted]
^{177}Lu vs cabazitaxel (OS)	[redacted]	[redacted]

Abbreviations: ^{177}Lu: ^{177}Lu vipivotide tetraxetan; CrI: credible interval; OS: overall survival; rPFS: radiographic progression-free survival.

The results presented above indicate an OS and rPFS benefit for ^{177}Lu vipivotide tetraxetan compared to cabazitaxel, and corroborate the expected treatment effect

	elicited from the clinical experts. This analysis is however associated with some limitations: • Time to progression on an ARPI was not a stratification factor in the VISION trial, therefore the subgroup analysis of the VISION trial focusing on patients who progressed within 12 months of receipt of a prior ARPI breaks randomisation. As shown in Table 10 in Appendix 3, baseline characteristics were reasonably well-matched across treatment arms, but given the lack of randomisation, observed or unobserved differences in patient characteristics across treatment arms could contribute to differences in observed treatment outcomes, and thereby confound the results of the Bucher ITC. • There are very low patient numbers in the subgroup of the VISION trial who progressed within 12 months of initiation of ARPI treatment, suggesting a poor overlap in patient populations between VISION and CARD, and resulting in wide confidence intervals. Given this subgroup analysis breaks randomisation, adjusting for differences in patient characteristics across the VISION treatment arms was considered, but was not feasible given the already small patient numbers available for adjustment. • Finally, there is an important distinction between treatment with an ARPI as part of SOC in the VISION trial, and as part of the control arm of CARD. Patients in VISION were prescribed ARPI as part of SOC based on clinical judgement, likely where there may be an expectation of additional clinical benefit. In contrast, patients receiving a second ARPI was mandated in the control arm of CARD,[4] regardless of any anticipated clinical benefit and disease progression within 12 months of treatment with an ARPI, typically associated with rapid ARPI resistance. Indeed, clinical expert feedback during the Committee meeting indicated that the CARD trial demonstrated a lack of clinical benefit associated with *retreatment* with ARPIs, specifically in patients who are likely to have rapidly developed ARPI resistance (within 12 months of treatment with a prior ARPI).[2] This suggests that the control arms of the two trials are heterogeneous in their treatment intentions, and thus the treatment effects derived from each trial are not comparable. Administration of a second ARPI as performed in the CARD trial control arm deviates significantly from NHS clinical and reimbursement practice which limits comparability of the CARD trial control arm with UK clinical practice. Given the numerous limitations, it remains a significant challenge to further reduce uncertainty associated with estimation of comparable relative treatment effects between the interventions of interest (^{177}Lu vipivotide tetraxetan and cabazitaxel) and a second ARPI which form the basis of any anchored ITC. **An unanchored MAIC was performed between the intervention arms of the CARD and VISION trials, derived from a larger number of patients and adjusting for important differences in patient characteristics between the two trials**

In order to provide the Committee with further evidence for relative efficacy between ^{177}Lu vipivotide tetraxetan and cabazitaxel, an alternative indirect comparison of the CARD and VISION trial was conducted. In order to maximise patient numbers available to adjust for differences in variables across the two trials, a unanchored MAIC was carried between the intervention arms of the CARD trial (n=129) and the *ARPI-subgroup population* of the VISION trial (n=243).

The MAIC adjusted for differences in key prognostic factors and treatment effect modifiers between the two studies, as identified via a systematic literature review (SLR) of prognostic variables and confirmed through clinical expert opinion.[2, 8] The variables adjusted for in the MAIC analysis included proportion of patients with ECOG performance status of 0 to 1, presence of liver or lung metastases, presence of bone metastases, proportion of patients who had received docetaxel before ARPI, median age and proportion of patients with Gleason score of 8 to 10. The rPFS and OS HRs (before and after weighting) for ^{177}Lu vipivotide tetraxetan versus cabazitaxel are shown in Table 3. Full details of the methods and results of the MAIC are provided in Appendix 4.

Table 3: rPFS and OS hazard ratios before and after weighing for ^{177}Lu vipivotide tetraxetan versus cabazitaxel (unanchored MAIC between CARD and VISION)

	Before weighting		After weighting	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
^{177}Lu vs cabazitaxel (rPFS)	[redacted]	[redacted]	[redacted]	[redacted]
^{177}Lu vs cabazitaxel (OS)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; MAIC: matching-adjusted indirect comparison; OS: overall survival; rPFS: progression-free survival.

The results of the MAIC corroborate previously presented analyses, with ^{177}Lu vipivotide tetraxetan showing [redacted] survival benefits as compared to cabazitaxel, both for rPFS and OS. Whilst this unanchored comparison remains susceptible to bias from unobserved confounding, this analysis presents various advantages:

- This analysis is based on larger patient numbers, including patients in the intervention arms of CARD and the subpopulation of patients who received ARPI as part of SOC in VISION. This analysis does not adjust for differences in the time to progression on a prior ARPI, but the impact of this effect modifier on outcomes for sequential ARPI no longer biases the estimate of relative effect (the impact of ARPI resistance is likely to have a greater impact on outcomes for sequential ARPI than outcomes for cabazitaxel). Accordingly, whilst highlighting differences in *relative* efficacy, Watson *et al.* (2022) suggests that median OS for cabazitaxel is similar between those who progress within 12 months or prior ARPI initiation and those who progress after 12 months (16.9 months and 17.1, respectively).[3]
- Focusing on trial populations is likely to minimise differences in prognosis compared with the propensity score weighting (PSW) analysis presented at

	Technical Engagement between VISION and the cabazitaxel RWE, and better reporting of characteristics permits more comprehensive adjustment for observed differences in prognostic variables and treatment effect modifiers. Given the greater sample sizes and smaller confidence intervals associated with the unanchored MAIC as compared to the Bucher ITC described above, the MAIC was chosen to inform relative efficacy for OS between [177]Lu vipivotide tetraxetan and cabazitaxel in the Company's revised base case analysis. Given the similarity in HRs for rPFS, the HR derived from the ERG-preferred NMA informed relative efficacy for [177]Lu vipivotide tetraxetan versus cabazitaxel for rPFS in the revised base case, but the HR for rPFS from the unanchored MAIC was explored in a scenario. The updated base case analysis results are shown in Appendix 1 below.
2	**In line with the Committee's preference, the RWE OS data informs the absolute efficacy of cabazitaxel in the model, with a HR derived from the anchored MAIC used to estimate survival for [177]Lu vipivotide tetraxetan** Following ACM2, the Committee reiterated its preference for using the RWE data to estimate absolute OS for cabazitaxel, with a HR derived from the NMA to estimate relative efficacy of [177]Lu vipivotide tetraxetan. The Company note that the VISION trial represents the most reliable source for estimating survival for [177]Lu vipivotide tetraxetan in the model. As per the Company response to the first ACD, the parametric model selected for extrapolating [177]Lu vipivotide tetraxetan OS (Stratified flexible Weibull [2 knots]) was closely aligned to clinical expert predictions of OS for patients receiving [177]Lu vipivotide tetraxetan in UK clinical practice, who estimated survival to be between 9–16% at three years, and 4–8% at four years for [177]Lu vipivotide tetraxetan; the Stratified flexible Weibull (2 knots) model predicts [redacted]% and [redacted]% survival for [177]Lu vipivotide tetraxetan at three and four years, respectively.[11] However, in order to align with the Committee's preferred analysis, the Company's revised base case uses the cabazitaxel RWE OS data to inform absolute efficacy of cabazitaxel in the model. As outlined in the response to Key Issue 1 above, the unanchored MAIC provides a more reliable estimate of relative efficacy between [177]Lu vipivotide tetraxetan and cabazitaxel. As aforementioned, the re-analysis of RWE PSW is underway which is anticipated to provide further evidence for relative efficacy. The HR derived from the unanchored MAIC analysis has therefore been applied to the cabazitaxel RWE OS curve, in order to estimate relative OS efficacy of [177]Lu vipivotide tetraxetan in the model. This analysis results in an incremental life-year gain of a [redacted] between [177]Lu vipivotide tetraxetan and cabazitaxel, which is substantially greater than the 3-month life extension required to meet NICE's end-of-life criteria. The Company's revised base case cost-effectiveness estimates are presented in Appendix 1, and clearly demonstrates [177]Lu vipivotide tetraxetan to be a cost-effective use of NHS resources at a WTP threshold of £50,000 for end-of-life medicines.

	For completeness, in order to provide the Committee with results of it's preferred analyses at the second ACM, a scenario analysis has been presented in which both OS and rPFS are based on the ERG-preferred NMA, the results of which can be found in Table 1, Appendix 2. The Company reiterates that this scenario assumes no difference in OS between treatments, and therefore lacks clinical validity. The results should therefore be interpreted with a high degree of caution.
3	**The Company maintain that a robust comparison of the cost-effectiveness of ^{177}Lu vipivotide tetraxetan versus radium-223 is not feasible. Furthermore, the two treatments are likely to be considered in different patient populations, with radum-223 representing a potential comparator in a small number of patients. The Company have therefore not included radium-223 as a comparator in its revised economic analysis** As noted throughout the submission process, radium-223 is not considered a relevant comparator in this appraisal for the following reasons: • Strict eligibility criteria for the presence of bone metastases and absence of visceral metastases mean that the overlap in patient populations eligible for both ^{177}Lu vipivotide tetraxetan and radium-223 is likely to be small. As more sensitive PSMA-imaging becomes more widely used in clinical practice, and more visceral metastases are identified, the number of patients eligible for both radium-223 and ^{177}Lu vipivotide tetraxetan is likely to become smaller still. • Clinical feedback received as part of ACD2 response noted that whilst some patients unfit for 3rd-line cabazitaxel may receive radium-223, only a small number of patients do so post-docetaxel and post-ARPI. This is confirmed by RWE data, indicating that only [redacted]% of patients with mCRPC having received prior docetaxel and ARPI (n=[redacted]) went on to receive radium-223 (n=[redacted]). • The clinical lead for the Cancer Drugs Fund noted that, in England, around 700 people start radium-223 each year compared with around 1,000 people starting cabazitaxel. However, [redacted] of patients who were recorded to have received radium-223 in the RWE dataset did so following treatment with prior docetaxel and ARPI, suggesting that the use of radium-223 in clinical practice is not fully aligned with the positioning of ^{177}Lu vipivotide tetraxetan. Further to the small overlap in patient populations between ^{177}Lu vipivotide tetraxetan and radium-223, a robust comparison in the population of interest is not feasible. Heterogeneity between the CARD and ALSYMPCA trials, notably that the ALSYMPCA trial only enrolled ARPI-naïve patients, means that a robust estimate of the relative treatment effect for OS between radium-223 and ^{177}Lu vipivotide tetraxetan cannot be derived. In addition, the ALSYMPCA trial did not report rPFS, so no comparison for this outcome can be performed. Accordingly, a comparison versus radium-223 was not considered feasible in the recent NICE appraisal of olaparib in a similar indication (adults with hormone-relapsed metastatic prostate cancer with BRCA1 or BRCA2 mutations that

	has progressed after an ARPI), and thus the exclusion of radium-223 as a comparator was considered acceptable by the ERG.[12] The Company have been unable to source alternative data to inform a robust comparison to radium-223 and ^{177}Lu vipivotide tetraxetan is unlikely to be used in a comparable population. The Company therefore maintain that radium-223 cannot be included as a comparator in this submission, and that its exclusion does not represent a major source of uncertainty.
4	**The base case analysis is generalisable to patients medically unsuitable for taxanes** Patients medically unsuitable for taxanes face limited treatment options, and therefore the introduction of ^{177}Lu vipivotide tetraxetan would address the high unmet need for a new, innovative and well-tolerated treatment in this population. Clinician feedback has repeatedly confirmed that ^{177}Lu vipivotide tetraxetan is anticipated to be equally efficacious in this patient population as it is in patients previously treated with taxanes. The Committee notes clinical feedback that prognosis in patients medically unsuitable for taxanes may be poorer than in those patients able to receive taxane-based chemotherapy. However, as per the Company responses throughout the post-submission process, the current poor prognosis for patients not medically suitable for taxanes is a result of the lack of effective treatment options, and therefore may not be a good predictor of the ability of such patients to respond to treatment with ^{177}Lu vipivotide tetraxetan. Many factors informing suitability for taxanes relate to the risks associated with taxane treatment, given their substantial toxicity, and not the ability of the patient to respond to treatment. Furthermore, the patient population of interest (beyond those medically unsuitable for taxanes) is for patients having received *and subsequently progressed* on a taxane. Failure of prior taxane therapy is an important prognostic factor, and thus patients medically unsuitable for taxanes may in fact have an *improved* comparative prognosis on ^{177}Lu vipivotide tetraxetan than patients who have received and failed treatment with docetaxel. This is corroborated by literature evidence identified by the Company: a retrospective study published by Ahmadzadehfar *et al.* (2021) investigated the prognostic impact of prior therapies in patients receiving ^{177}Lu vipivotide tetraxetan and showed that patients who had received prior chemotherapy had poorer survival outcomes than patients who had not.[13] It also showed that there was no difference in OS between patients who had not received chemotherapy and patients for whom chemotherapy was contraindicated.[13] Studies published by Khreish *et al.* (2022) and Barber *et al*. (2019) also support better outcomes for patients receiving ^{177}Lu vipivotide tetraxetan in patients who have not previously received taxanes,[14, 15] as does a recent systematic literature review and NMA published by Satapathy *et al.* (2023).[16]

	In order to explore the uncertainty in the prognosis of this patient population, the Company has explored additional scenario analyses for the comparison of ^{177}Lu vipivotide tetraxetan versus SOC. In line with the evidence from the literature, a decreased hazard of progression and death was applied to rPFS and OS, respectively, to reflect a better prognosis in the ^{177}Lu vipivotide tetraxetan and SOC arms. The hazard explored in this scenario was informed by the hazard ratio reported in the Ahmadzadehfar *et al.* (2021) study between the subgroups having received prior taxane therapy and those having no prior history of taxane-based chemotherapy. Weighted HRs were calculated from the results of univariate and multivariate analyses performed in Ahmadzadehfar *et al.* (2021) to more closely reflect the patient population in the VISION trial (based on the proportions of patients in VISION with 1 or 2 prior taxanes). Both the weighted HRs resulting from the univariate (HR = 0.649) and multivariate (HR = 0.673) analyses were applied in separate analyses. Ahmadzadehfar *et al.* (2021) was chosen to inform this analysis given its larger sample size compared with other studies identified. The resulting cost-effectiveness estimates for ^{177}Lu vipivotide tetraxetan versus SOC are presented in Appendix 2, and show ^{177}Lu vipivotide tetraxetan to have improved cost-effectiveness versus SOC when better prognosis is modelled. The Company acknowledges limitations in using evidence from a patient population who have not received prior taxane-based chemotherapy as a proxy for a patient population unsuitable for taxanes and thus an assumption of no difference in efficacy is maintained in the base case analysis. However, as indicated by clinical feedback, medical unsuitability is highly heterogenous, and a significant number of patients would be unsuitable due to personal choice, rather than their medical profile; evidence from pre-taxane patient populations is likely to be generalisable to this patient population. Furthermore, evidence suggests that no difference in OS for ^{177}Lu vipivotide tetraxetan would be expected between patients who have not received chemotherapy and patients for whom chemotherapy is contraindicated (e.g. patients with substantial comorbidities).[13] Therefore, the results of these scenarios are relevant and have been presented in Appendix 2 for the Committee's consideration.
5	**Additional scenarios exploring revised cabazitaxel adverse event (AE) incidence and duration support the use of treatment-dependent utility values** Patient and clinical experts present during ACM2 noted that persistent grade 2 adverse events associated with chemotherapy can have debilitating effects on patients. Advisors highlighted that one such AE is fatigue; the patient expert explained that it took them 12 to 18 months to fully recover from fatigue experienced following treatment with prior taxane-based chemotherapy, whilst they only experienced fatigue for a week following treatment with ^{177}Lu vipivotide tetraxetan. Grade 2 neuropathy was also noted as a persistent issue associated with chemotherapy heavily impacting patients' QoL. The Committee acknowledged this, and noted its preference to consider scenarios using treatment-independent utility values where the impact of these grade 2 adverse events was included. The Company originally only included disutilities associated with grade ≥3

	AEs in scenario analyses where treatment-independent utility values were used. Treatment-independent utility values were not used in the base case because this approach is unlikely to fully account for patients' experience of treatment, in particular with cabazitaxel. The Company has conducted three additional scenario analyses using treatment-independent utility values and AE utility decrements with revised assumptions regarding AEs for fatigue and neuropathy: • Treatment-independent utility values were applied and only grade ≥3 AEs were included for ^{177}Lu vipivotide tetraxetan and cabazitaxel (as per original treatment-independent utility scenarios). The duration of disutility for fatigue and neuropathy AEs for cabazitaxel was aligned with treatment duration from CARD (5.06 months), in line with clinical and patient feedback.[17] • Treatment-independent utility values were applied and all-grade neuropathy and fatigue/asthenia AEs were included for ^{177}Lu vipivotide tetraxetan and cabazitaxel. The same utility decrement was applied regardless of grade (in the absence of a reported disutility for grade 1–2 AEs), and no change in AE duration was modelled (i.e. a duration of 1 month modelled for both interventions). • Treatment-independent utility values were applied and all-grade neuropathy and fatigue/asthenia AEs were included for ^{177}Lu vipivotide tetraxetan and cabazitaxel. The same utility decrement was applied regardless of grade (in the absence of a reported disutility for grade 1–2 AEs), and the duration of disutility for these AEs for cabazitaxel was aligned with treatment duration reported in CARD, in line with clinical and patient feedback[17] Incidence of grade 2 AEs were not reported separately in the CARD and VISION trials, and thus all-grade fatigue and neuropathy were used in the final two scenarios (Table 4). A disutility for grade 1–2 AEs could not be sourced, and thus the same utility decrements for all-grade AEs were assumed (Table 5); this is unlikely to hold true in practice, but these scenarios still demonstrate the sensitivity of the cost-effectiveness results to assumptions around the persistence of these low-grade AEs.

Table 4: AE incidence rates explored in scenarios

AE	Cabazitaxel		^{177}Lu vipivotide tetraxetan	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Asthenia	53.2%	4.0%	6.4%	1.1%
Fatigue			43.1%	5.9%
Peripheral neuropathy	19.8%	3.2%	[redacted]%[a]	[redacted]%[a]

[a]Includes peripheral sensory, peripheral motor, peripheral sensorimotor, neuropathy peripheral.
Abbreviations: AE: adverse event
Source: Advanced Accelerator Applications Data on File (VISION).[18] de Wit *et al* (2019).[4]

Table 5: Utility decrements associated with AEs explored in scenarios

AE	Disutility	Source
Asthenia or fatigue	0.12	Lloyd et al. (2006)[19]
Peripheral neuropathy	0.145	NICE TA259 (2012)[20]

Abbreviations: AE: adverse event; NICE: National Institute of Health and Care Excellence.

The cost-effectiveness results for these scenarios are presented in Table 9 in Appendix 2. Modelling these persistent AEs noted during ACM2 produces results consistent with the Company's base case analysis using treatment-dependent utility values to account for differences in QoL experienced by patients receiving different treatments. This provides reassurance that the treatment-dependent approach to utility values is a valid and robust method of estimating differences in QoL in the model. Whilst these updated treatment-independent utility scenarios are more representative than those previously presented at technical engagement and preferred by the ERG, the Company maintain that this approach cannot account for all important differences in QoL between treatments. In particular, the psychological burden of receiving further cytotoxic taxane-based chemotherapy or receiving inactive treatment, associated with cabazitaxel and SOC respectively, are important factors not captured in these analyses. The Company therefore maintain that treatment-dependent utility values are most appropriate, and have therefore been retained in the Company's base case economic analysis.

6

The costs of PSMA testing accounted for in the model have been aligned to the Committee's preference, following clinical feedback received at ACM2

Feedback from the clinical lead for the Cancer Drugs Fund received as part of ACD2 indicated that accounting for 50–75% of patients in ^{177}Lu vipivotide tetraxetan arm incurring additional costs associated with PSMA testing was most reflective of variation in access to routine testing across England and Wales. The Committee agreed with this estimate.

In order to align with the Committee's preference, the Company has updated its base case economic analysis, in which 62.5% of patients in ^{177}Lu vipivotide tetraxetan arm are modelled as incurring PSMA testing costs, the midpoint between the Committee's preferred lower and upper estimates (50% and 75%, respectively). The Committee's

	upper and lower estimates have been explored in scenario analyses presented in Appendix 2. Varying the proportion of patients incurring PSMA testing costs in the ^{177}Lu vipivotide tetraxetan arm in the model has minimal impact on cost-effectiveness estimates, with all results showing ^{177}Lu vipivotide tetraxetan to be a cost-effective treatment option for the NHS at a WTP threshold of £50,000.

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^{177}Lu vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]

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Appendix 1 Updates to Company base case

In this response to the second ACD2, the Company has updated the base case analysis as follows:

- In the comparison of ^{177}Lu vipivotide tetraxetan with cabazitaxel, the OS estimates for cabazitaxel derived from the RWE study have been used as the reference, to which a HR has been applied to derive OS estimates for ^{177}Lu vipivotide tetraxetan. Note, in the comparison of ^{177}Lu vipivotide tetraxetan with SOC, the VISION trial data are used directly.
- Trials that enrolled exclusively ARPI-naïve patients were excluded from the new ITC informing relative efficacy between ^{177}Lu vipivotide tetraxetan and cabazitaxel. Instead, the relative effect for OS between ^{177}Lu vipivotide tetraxetan and cabazitaxel is based on an unanchored MAIC between the ARPI-subgroup intervention arms of the VISION and CARD trials.
- PSMA testing costs have been applied to 62.5% of patients in the ^{177}Lu vipivotide tetraxetan arm, selected as the midpoint between the range considered reflective of variation in access to routine testing across England and Wales by the clinical lead for the Cancer Drugs Fund (50–75%).
- In line with the ERG's ACD preferred analysis, the model updates included: Inclusion of fixes (EA1f-EA3), correction of admin costs for SOC (EA4), treatment mean (not median) for ^{177}Lu vipivotide tetraxetan (EA4), ERG's preferred NMA estimates (EA10 & EA12) (the OS HR is explored in a scenario)
- In line with the ERG's ACD preferred analysis, the ^{177}Lu vipivotide tetraxetan unit cost includes PET-CT scan costs and use of the Company's original VISION utility analysis

Table 6: Revised Company base case results for ^{177}Lu vipivotide tetraxetan versus cabazitaxel at ^{177}Lu vipivotide tetraxetan PAS price (deterministic)

Intervention	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
^{177}Lu vipivotide tetraxetan	[redacted]	[redacted]	[redacted]				
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	38,567

Abbreviations: ^{177}Lu: Lutetium-177; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 7: Revised Company base case results for ^{177}Lu vipivotide tetraxetan versus SOC at ^{177}Lu vipivotide tetraxetan PAS price (deterministic)

Intervention	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
^{177}Lu vipivotide tetraxetan	[redacted]	[redacted]	[redacted]				
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	123,016

Abbreviations: ^{177}Lu: Lutetium-177; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALY: quality-adjusted life year; SOC: standard of care.

Appendix 2 Additional scenario analysis results

Deterministic cost-effectiveness results for ^{177}Lu vipivotide tetraxetan versus cabazitaxel and SOC, resulting from a number of scenarios explored as part of the Company's response to the ACD2, are presented in Table 8 and Table 9, respectively, below.

Table 8: Results of the scenario analysis at ^{177}Lu vipivotide tetraxetan PAS price versus cabazitaxel (deterministic)

Scenario	Description	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Base case		[redacted]	[redacted]	38,567
1	Alternative OS HR for ^{177}Lu vipivotide tetraxetan versus cabazitaxel: 0.7176 derived from the unanchored comparison before weighting	[redacted]	[redacted]	52,260
2	OS HR for ^{177}Lu vipivotide tetraxetan versus cabazitaxel: 0.6375 and rPFS HR for ^{177}Lu vipivotide tetraxetan versus cabazitaxel: 0.7415 derived from the unanchored MAIC	[redacted]	[redacted]	38,523
3	OS HR for ^{177}Lu vipivotide tetraxetan versus cabazitaxel: 0.7176 and rPFS HR for ^{177}Lu vipivotide tetraxetan versus cabazitaxel: 0.8045 derived from the unanchored MAIC	[redacted]	[redacted]	52,388
4	Alternative OS HR for ^{177}Lu vipivotide tetraxetan versus cabazitaxel: 0.9983 derived from EAG preferred NMA	[redacted]	[redacted]	369,593
5	Treatment-independent utility values: grade ≥3 neuropathy and fatigue with disutility duration for cabazitaxel aligned to mean treatment duration from CARD	[redacted]	[redacted]	39,934
6	Treatment-independent utility values: all-grade neuropathy and fatigue with disutility duration unchanged	[redacted]	[redacted]	38,206
7	Treatment-independent utility values: all-grade neuropathy and fatigue with disutility duration for cabazitaxel aligned to mean treatment duration from CARD	[redacted]	[redacted]	34,896
8	PSMA testing costs assumed to be incurred by 50% of patients in the ^{177}Lu vipivotide tetraxetan arm of the model	[redacted]	[redacted]	38,202
9	PSMA testing costs assumed to be incurred by 75% of patients in the ^{177}Lu vipivotide tetraxetan arm of the model	[redacted]	[redacted]	38,931

Abbreviations: ^{177}Lu: Lutetium-177; AE: adverse event; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; PSMA: prostate-specific membrane antigen; QALY: quality-adjusted life year.

Table 9: Results of the scenario analysis at ^{177}Lu vipivotide tetraxetan PAS price versus SOC (deterministic)

Scenario	Description	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Base case		[redacted]	[redacted]	123,016
1	Decreased hazard of progression and death applied to both model arms as a proxy for better prognosis in medically unsuitable population, based on Ahmadzadehfar *et al.* (2021) univariate analysis (weighted HR = 0.649)	[redacted]	[redacted]	86,008
2	Decreased hazard of progression and death applied to both model arms as a proxy for better prognosis in medically unsuitable population, based on Ahmadzadehfar *et al.* (2021) multivariate analysis (weighted HR = 0.673)	[redacted]	[redacted]	88,621

Abbreviations: ^{177}Lu: Lutetium-177; AE: adverse event; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; PSMA: prostate-specific membrane antigen; QALY: quality-adjusted life year; SOC: standard of care.

Appendix 3 Bucher ITC

VISION subgroup analysis: patients who progressed ≤12 months of receipt of a prior ARPI

In order to address the limitations of the network meta-analyses informing the ERG and Company analyses and align with Committee preference, in particular addressing the heterogeneity in eligibility criteria across the VISION and CARD trials, a subgroup analysis of the VISION trial was explored for the purposes of exploring a Bucher ITC. The subgroup includes patients from the VISION trial who meet the eligibility criteria for CARD, i.e. those patients who had progressed within 12 months of receipt of a prior ARPI, thereby reducing differences between trials in this important treatment effect modifier.

Table 10: Baseline characteristics for VISION subgroup who progressed ≤12 months of receipt of a prior ARPI (PFS-FAS and FAS)

Characteristic	PFS-FAS; progressed ≤12 months of receipt of a prior ARPI (N = [redacted])		FAS; progressed ≤12 months of receipt of a prior ARPI (N = [redacted])	
	^{177}Lu vipivotide tetraxetan + SOC-ARPI (N=[redacted])	SOC-ARPI (N=[redacted])	^{177}Lu vipivotide tetraxetan + SOC-ARPI (N=[redacted])	SOC-ARPI (N=[redacted])
Median age (range), years	[redacted]	[redacted]	[redacted]	[redacted]
ECOG ≤1, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Site of disease, n (%)				
Lung	[redacted]	[redacted]	[redacted]	[redacted]
Liver	[redacted]	[redacted]	[redacted]	[redacted]
Lymph node	[redacted]	[redacted]	[redacted]	[redacted]
Bone	[redacted]	[redacted]	[redacted]	[redacted]
Median PSA level (range), ng/ml	[redacted]	[redacted]	[redacted]	[redacted]
Median alkaline phosphatase level (range), IU/litre	[redacted]	[redacted]	[redacted]	[redacted]
Median LDH (range), IU/litre	[redacted]	[redacted]	[redacted]	[redacted]
Median time since diagnosis (range), years	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ^{177}Lu: Lutetium-177; ARPI: androgen receptor pathway inhibitor; ECOG: Eastern Cooperative Oncology Group; FAS: full analysis set; IU: international unit; PFS-FAS: progression-free survival full analysis set; LDH: lactate dehydrogenase; PSA: prostate specific antigen; PSMA: prostate-specific membrane antigen; SOC standard of care.

Table 11: OS in VISION subgroup who progressed ≤12 months of receipt of a prior ARPI (FAS)

	^{177}Lu vipivotide tetraxetan + SOC-ARPI (N=[redacted])	SOC-ARPI (N=[redacted])
Deaths	[redacted]	[redacted]
Censored	[redacted]	[redacted]
Alive	[redacted]	[redacted]

Lost to follow-up	[redacted]	[redacted]
Withdrew consent	[redacted]	[redacted]
Median OS [99.2% CI]	[redacted]	[redacted]
OS rates (%)		
3 months (SE) [99.2% CI]	[redacted]	[redacted]
6 months (SE) [99.2% CI]	[redacted]	[redacted]
12 months (SE) [99.2% CI]	[redacted]	[redacted]
Log-Rank test and Cox regression model		
HR (99.2% CI)[a,b]	[redacted]	
Follow-up time (months)[c]		
Median [95% CI]	[redacted]	[redacted]
Minimum, Maximum	[redacted]	[redacted]

[a]Hazard Ratio of [177]Lu vipivotide tetraxetan + SOC vs. SOC from stratified Cox PH model. [b]Both Cox PH model and Log-rank test are stratified for LDH (≤ 260 IU/L vs. > 260 IU/L); presence of liver metastases (yes vs. no); ECOG score (0 or 1 vs. 2); and inclusion of ARPI in best supportive/standard of care at time of randomisation (yes vs no). IRT data for stratification are used.
[c]Follow-up time = (Date of event or censoring - randomisation date + 1)/30.4375 (months) censoring for deaths.
Abbreviations: [177]Lu: Lutetium-177; CI: confidence interval; FAS: full analysis set; IRT: interactive response technology; NE: not evaluable; OS: overall survival; PH: proportional hazards; PSMA: prostate-specific membrane antigen; SE: standard error.

Figure 1: Kaplan–Meier plot of OS in VISION subgroup who progressed ≤12 months of receipt of a prior ARPI (FAS)

Stratified log-rank test and stratified Cox model using strata per Interactive Response Technology defined by LDH level, presence of liver metastases, ECOG score and inclusion of ARPI in SOC at time of randomisation.
n/N: number of events/number of patients in treatment arm.
Abbreviations: [177]Lu: Lutetium-177; ARPI: androgen receptor pathway inhibitor; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; FAS: full analysis set; LDH: lactate dehydrogenase; OS: overall survival; PSMA: prostate-specific membrane antigen; SOC: standard of care.

^{177}Lu vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]

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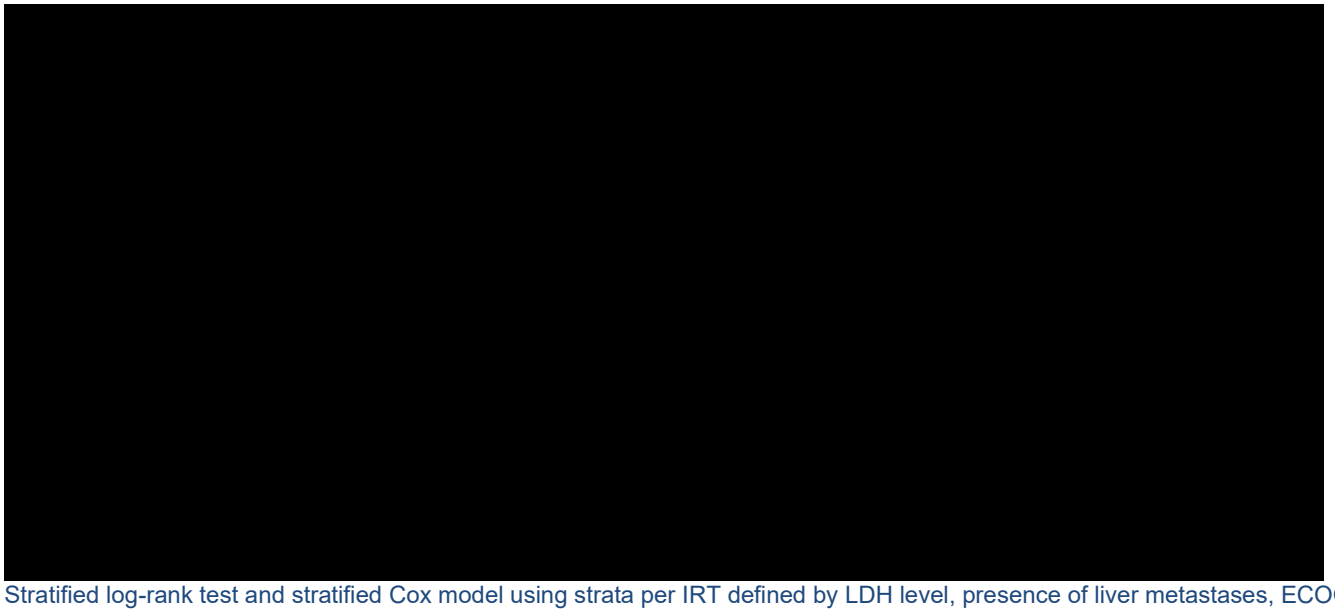
Table 12: rPFS in VISION subgroup who progressed ≤12 months of receipt of a prior ARPI (PFS-FAS)

	^{177}Lu vipivotide tetraxetan + SOC-ARPI (N=[redacted])	SOC-ARPI (N=[redacted])
Events	[redacted]	[redacted]
Radiographic progressions	[redacted]	[redacted]
Deaths	[redacted]	[redacted]
Censored	[redacted]	[redacted]
Ongoing without event	[redacted]	[redacted]
Event documented after 2 or more missed tumour assessments	[redacted]	[redacted]
Adequate assessment not available	[redacted]	[redacted]
Median rPFS [99.2% CI]	[redacted]	[redacted]
rPFS rates (%)		
3 months (SE) [99.2% CI]	[redacted]	[redacted]
6 months (SE) [99.2% CI]	[redacted]	[redacted]
12 months (SE) [99.2% CI]	[redacted]	[redacted]
Log-Rank test and Cox regression model		
HR (99.2% CI)[a,b]	[redacted]	
Follow-up time (months)[d]		
Median [95% CI]	[redacted]	[redacted]
Minimum, Maximum	[redacted]	[redacted]

[a]Hazard Ratio of ^{177}Lu vipivotide tetraxetan + SOC vs. SOC only. [b]Both Cox PH model and Log-rank test are stratified for LDH (≤ 260 IU/L vs. > 260 IU/L); presence of liver metastases (yes vs. no); ECOG score (0 or 1 vs. 2); and inclusion of ARPI in SOC at time of randomisation (yes vs no). IRT data for stratification are used. [c]Patients censored without adequate post-baseline evaluations or adequate baseline assessment. [d]Follow-up time = (Date of event or censoring - randomisation date + 1)/30.4375 (months) censoring for death or radiographic progression.

Abbreviations: ^{177}Lu: Lutetium-177; CI: confidence interval; IRT: interactive response technology; NE: not evaluable; PFS-FAS: progression-free survival full analysis set; PH: proportional hazards; PSMA: prostate-specific membrane antigen; rPFS: radiographic progression-free survival; SE: standard error.

Figure 2: Kaplan–Meier plot of rPFS in VISION subgroup who progressed ≤12 months of receipt of a prior ARPI per independent central review (PFS-FAS)



Stratified log-rank test and stratified Cox model using strata per IRT defined by LDH level, presence of liver metastases, ECOG score and inclusion of ARPI in SOC at time of randomisation.
n/N: number of events/number of patients in treatment arm.
Abbreviations: ^{177}Lu: Lutetium-177; ARPI: androgen receptor pathway inhibitor; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; IRT: interactive response technology; PFS-FAS: progression-free survival full analysis set; LDH: lactate dehydrogenase; PSMA: prostate-specific membrane antigen; rPFS: radiographic progression-free survival; SOC: standard of care.

Bucher ITC versus CARD

Methods

Given the common comparator ARPI arm in the ARPI subgroup population of the VISION trial and CARD trial, a Bucher ITC was carried out to conduct a naïve comparison of ^{177}Lu vipivotide tetraxetan and ARPI to cabazitaxel.

Results

Table 13: rPFS and OS estimates for ^{177}Lu versus cabazitaxel (Bucher ITC between CARD and VISION)

Scenario	HR	95% CI
OS: ^{177}Lu vipivotide tetraxetan versus cabazitaxel	[redacted]	[redacted]
rPFS: ^{177}Lu vipivotide tetraxetan versus cabazitaxel	[redacted]	[redacted]

Abbreviations: ^{177}Lu: ^{177}Lu vipivotide tetraxetan; CI: confidence interval; ITC: indirect treatment comparison; KM; Kaplan-Meier; OS: overall survival; rPFS: radiographic progression-free survival.

Appendix 4 Unanchored MAIC

In order to maximise patient numbers available for adjustment of differences in variables across the two trials, a MAIC was carried between the CARD trial and the *overall population* of the VISION trial.

Methods

Selection of variables for adjustment

To determine which variables should be adjusted for in the unanchored MAIC, the status for each variable as a prognostic factor and effect modifier was examined. An SLR was performed to identify prognostic factors in mCRPC, and clinical feedback was sought to confirm the importance of key baseline characteristics available from the VISION and CARD trials as prognostic factors or treatment effect modifiers.[2, 8] Based on the SLR and in line with clinical feedback received, the following baseline characteristics were selected for inclusion in the MAIC:

- The proportion of patients with ECOG performance status of 0–1
- The presence of liver or lung metastases
- The presence of bone metastases
- The proportion of patients who had received docetaxel before ARPI
- Median Age
- The proportion of patients with Gleason score 8–10

Analytic approach

An unanchored MAIC was conducted in line with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18,[21] using individual patient data from the ^{177}Lu vipivotide tetraxetan arm of the VISION trial and published data from the cabazitaxel arm of the CARD trial.

A propensity score weighting approach was taken where patients in the ^{177}Lu vipivotide tetraxetan arm of the VISION trial were assigned weights such that the weighted mean baseline characteristics were comparable to those reported for the cabazitaxel arm of CARD. The analysis involved estimating a logistic propensity score model that was conditional on prognostic factors and effect modifiers identified in the previous step. This is equivalent to the following model on the dependent variable of log weight:

$$log(w_{it}) = \alpha_0 + \alpha_1^T X_{it}$$

where α is a vector of covariates that predict weight, and X_{it}^{EM} is the patient characteristic. Given the unanchored nature of the comparison, both effect modifiers and prognostic factors were matched/adjusted; however, it should be noted that the inclusion of too many variables will reduce the effective sample size (ESS) and may inflate the standard error due to overmatching.

Weights were estimated using the method of moments approach to match the variable distributions between the two studies. This is equivalent to minimizing the following function:

$$\sum_{i,j} \exp\left(a_1^T X_{ii}^{EM}\right)$$

when $E[X_{ii}^{EM}] = 0$. For this condition to be satisfied, the variables included in the model were "centred" by subtracting the $E[X_{ii}^{EM}]$ in the target population, e.g., cabazitaxel, from the X_{ii}^{EM} in the ^{177}Lu vipivotide tetraxetan population.

To estimate a_1, the *fminsearch* function was used to minimise the method of moments function using Nelder-Mead simplex algorithm.

Weights were estimated for each patient in the study based on the fitted a_1, and each individual patient characteristics, X_{ii}^{EM}. The weights were rescaled such that they were relative to the original unit weights of each individual, e.g. if weight >1 then the patient has more weight, if <1 then less weight and if =1 then the individual has the same weight as prior to matching. The rescaled weights were plotted on a histogram to assess the spread of weights across the population. This was used to assess whether the matched population was dependent on a small number of patients with high weights, or whether the weights were more evenly spread across the population. Ideally, the matched population should be based on a broad sample, and not too heavily dependent on a small number of patients. The maximum ESS is equal to the original trial size and occurs if the patient characteristics of VISION and CARD are identical.

After matching, the baseline characterises selected for adjustment were exactly matched between the trials and the ESS was [redacted]. This represents approximately a [redacted]% reduction in sample size, suggesting there were no extreme weights used in the rebalancing. The rescaled weights range from [redacted] to [redacted]. The histogram of rescaled weights presented in Figure 3 demonstrates a lack of extreme weights, and no patients in the VISION were assigned zero weight.

Figure 3: Distribution of weights – ^{177}Lu vipivotide tetraxetan (VISION) versus cabazitaxel (CARD)

Results

Baseline characteristics

Patient baseline characteristics before and after weighting in the unanchored MAIC of VISION ^{177}Lu vipivotide tetraxetan versus the cabazitaxel arm of CARD are presented in Table 14. Before weighting, baseline characteristics were generally well-balanced across the treatment arms. After weighting, key baseline characteristics adjusted for were exactly matched across arms, with only small changes observed for unadjusted baseline characteristics, indicating that the treatment arms were broadly well-balanced.

Table 14: Baseline characteristics for ^{177}Lu vipivotide tetraxetan (VISION) versus cabazitaxel (CARD) before and after weighting in the unanchored MAIC

Baseline characteristic	Before weighting		After weighting	
	Cabazitaxel	^{177}Lu vipivotide tetraxetan	Cabazitaxel	^{177}Lu vipivotide tetraxetan
ECOG PS (0-1)[a]	95.3%	[redacted]	95.3%	[redacted]
Liver/Lung metastases[a]	16.3%	[redacted]	16.3%	[redacted]
Bone metastases[a]	81.4%	[redacted]	81.4%	[redacted]
Docetaxel before ARPI[a]	38.8%	[redacted]	38.8%	[redacted]
Median Age[a]	70	[redacted]	70	[redacted]
Gleason score 8–10[a]	56.6%	[redacted]	56.6%	[redacted]
Mean PSA, ng/ml	264.4	[redacted]	264.4	[redacted]
Mean alkaline phosphatase, IU/litre	226.6	[redacted]	226.6	[redacted]
Mean lactate dehydrogenase, IU/litre	331	[redacted]	331	[redacted]
Mean Haemoglobin, g/litre	122	[redacted]	122	[redacted]
Mean Neutrophil count per cu mm	5000	[redacted]	5000	[redacted]

[a]Variable included in adjustment
Abbreviations: ARPI: androgen receptor pathway inhibitor**;** ECOG: Eastern Cooperative Oncology Group; MAIC: matching-adjusted indirect comparison; PS: performance status; PSA: prostate-specific antigen.

OS and rPFS

Median OS for the cabazitaxel cohort was similar before and after weighting. Kaplan–Meier curves for OS before and after weighting are presented in Figure 4, showing similar survival profiles. These results suggest that differences in observed characteristics between the RWE cohort and VISION had minimal impact on OS. As is the case with any comparison of non-randomised treatment groups, this analysis may be subject to potential bias due to unobserved or unmeasurable confounding.

Table 15: OS and rPFS for 177Lu vipivotide tetraxetan (VISION) versus cabazitaxel (CARD) before and after weighting

Scenario	Before weighting		After weighting	
	HR (95% CI)	p-value	HR (95% CI)	p-value
OS: ^{177}Lu vipivotide tetraxetan versus cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]
rPFS: ^{177}Lu vipivotide tetraxetan versus cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]

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

The Kaplan–Meier survival plots for ^{177}Lu vipivotide tetraxetan (before and after weighting) versus cabazitaxel are shown for OS and rPFS in Figure 4 and Figure 5, respectively.

Figure 4: OS KM curves for ^{177}Lu vipivotide tetraxetan (before and after weighting) versus cabazitaxel (based on the MAIC between CARD and VISION)

^{177}Lu-PSMA = ^{177}Lu vipivotide tetraxetan
Abbreviations: KM: Kaplan-Meier; MAIC: matching-adjusted indirect comparison; OS: overall survival.

Figure 5: rPFS KM curves for ^{177}Lu vipivotide tetraxetan (before and after weighting) versus cabazitaxel (based on the MAIC between CARD and VISION)

^{177}Lu-PSMA = ^{177}Lu vipivotide tetraxetan
Abbreviations: KM: Kaplan-Meier; MAIC: matching-adjusted indirect comparison; rPFS: radiographic progression-free survival.

ID3840 company responses to EAG clarification questions about ACD2 response

(1) For the Bucher ITC, how were the subgroup of patients who had progressed within 12 months of receipt of a prior ARPI identified from the VISION trial? Was this data collected as a part of the patient baseline characteristics? For patients who had more than one ARPIs, how progression with 12 months of receipt of a prior ARPI was defined?

The exact derivation of time to progression on a prior androgen receptor pathway inhibitor (ARPI) in the VISION trial is being sourced by the company's statistics team, and will be provided as soon as it is available.

(2) Appendix 3 Table 11 and Table 12. Please provide the rationale for using 99.2% CI instead of the 95% CI.

The choice of 99.2% rather than 95% confidence intervals (CI) in the subgroup analysis of VISION was aligned to the pre-specified primary analysis of radiographic progression-free survival (rPFS) in the VISION trial (see section Table 9, Section B.2.3.3 of the company submission). This was erroneously applied to the subgroup analysis of overall survival (OS) presented in the company's second ACD response. However, these were converted to 95% CIs prior to use in the Bucher indirect treatment comparison (ITC) for OS. This difference therefore has no influence on the OS ITC results.

(3) Unanchored MAIC. What software was used for this analysis? How the standard error of the relative treatment effect was calculated (provide the package used if relevant)?

R (Version 4.1.1) was used to carry out the unanchored matching adjusted indirect comparison (MAIC) analysis. Through propensity matching, weights were allocated to each patient of the ^{177}Lu vivipotide tetraxetan arm. The cabazitaxel arm of the CARD trial was digitised and pseudo-individual patient data (IPD) generated using the Guyot algorithm.[1] IPD data for both the arms (^{177}Lu vivipotide tetraxetan arm IPD from the VISION trial along with weights and pseudo-IPD for the cabazitaxel arm from the CARD trial) were used in the weighted Cox PH analysis (using the survival package in R) to calculate the hazard ratio and 95% CI.

(3) The company confirmed that the weighted Cox PH analysis was used in the unanchored MAIC. Could the company confirm whether a robust standard error was used to calculate the 95% CI?

We used Cox proportional hazards regression model with Breslow methodology for tie handling to estimate 95% CI which is a robust estimator for standard error.

(4) Please confirm the sample size of the RWE cabazitaxel cohort used in the model.

The RWE cabazitaxel cohort used in the model is that originally presented in the company submission, which consisted of [redacted] patients having initiated cabazitaxel. [redacted] patients had no recorded follow up and were censored from the survival analysis used to inform the model.

References

1. Guyot P, Ades AE, Ouwens MJ, et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol 2012;12:9.

Lu vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]

Dear [redacted],

In reviewing your ACD response, the EAG has asked for clarification on a few points. Please could you provide responses to the following as soon as possible early next week?

(1) For the Bucher ITC, how were the subgroup of patients who had progressed within 12 months of receipt of a prior ARPI identified from the VISION trial? Was this data collected as a part of the patient baseline characteristics? For patients who had more than one ARPIs, how progression with 12 months of receipt of a prior ARPI was defined?

These data were derived specifically for this subgroup analysis. To identify progression on a prior ARPI (after first ARPI and before randomisation), the case report (CRF) data were used for three items, namely the earliest date of: Prostate Specific Antigen (PSA) PSA progression, bone progression or soft tissue progression. Given the analyses were conducted in the full analysis set (FAS) and progression-free survival FAS (PFS-FAS), death date was not included as all patients in these analysis sets did not die prior to randomisation.

Radiographic progression-free survival (rPFS) and overall survival OS outputs were then rerun on this subgroup of patients (progressed ≤12 months after first ARPI prior to randomisation). For rPFS, which was based on PFS-FAS, [redacted] patients were included in the analysis, and for OS, which was based on FAS, [redacted] patients were included. Patients with partial or missing ARPI dates were excluded, and no imputation of dates was performed.

(2) Appendix 3 Table 11 and Table 12. Please provide the rationale for using 99.2% CI instead of the 95% CI.

The choice of 99.2% rather than 95% confidence intervals (CI) in the subgroup analysis of VISION was aligned to the pre-specified primary analysis of radiographic progression-free survival (rPFS) in the VISION trial (see section Table 9, Section B.2.3.3 of the company submission). This was erroneously applied to the subgroup analysis of overall survival (OS) presented in the company's second ACD response. However, these were converted to 95% CIs prior to use in the Bucher indirect treatment comparison (ITC) for OS. This difference therefore has no influence on the OS ITC results. The results for the VISION subgroup analysis including 95% CIs are presented in Table 1 for reference.

Table 1: OS in VISION subgroup who progressed ≤12 months of receipt of a prior ARPI (FAS)

	^{177}Lu vipivotide tetraxetan + SOC-ARPI (N=[redacted])	SOC-ARPI (N=[redacted])
Deaths	[redacted]	[redacted]
Censored	[redacted]	[redacted]
Alive	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Withdrew consent	[redacted]	[redacted]
Median OS [95% CI]	[redacted]	[redacted]
OS rates (%)		
3 months [95% CI]	[redacted]	[redacted]
6 months [95% CI]	[redacted]	[redacted]
12 months [95% CI]	[redacted]	[redacted]
Log-Rank test and Cox regression model		
HR (95% CI)[a,b]	[redacted]	
Follow-up time (months)[c]		
Median [95% CI]	[redacted]	[redacted]
Minimum, Maximum	[redacted]	[redacted]

[a]Hazard Ratio of ^{177}Lu vipivotide tetraxetan + SOC vs. SOC from stratified Cox PH model. [b]Both Cox PH model and Log-rank test are stratified for LDH (≤ 260 IU/L vs. > 260 IU/L); presence of liver metastases (yes vs. no); ECOG score (0 or 1 vs. 2); and inclusion of ARPI in best supportive/standard of care at time of randomisation (yes vs no). IRT data for stratification are used. [c]Follow-up time = (Date of event or censoring - randomisation date + 1)/30.4375 (months) censoring for deaths.

Abbreviations: ^{177}Lu: Lutetium-177; CI: confidence interval; FAS: full analysis set; IRT: interactive response technology; NE: not evaluable; OS: overall survival; PH: proportional hazards; PSMA: prostate-specific membrane antigen; SE: standard error.

NICE National Institute for Health and Care Excellence

Lutetium-177 vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]

Consultation on the appraisal consultation document – deadline for comments 5pm on Tuesday 14 March 2023. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**British Nuclear Medicine Society (BNMS)**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None**]
Name of commentator person completing form:	[Sabina Dizdarevic]

Comment number	**Comments**

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	• **Has all of the relevant evidence been taken into account?** The BNMS believes that there is no single direct comparator for this innovative treatment appraisal. In the absence of adequately powered direct comparisons of ^{177}Lu vipivotide tetraxetan versus other treatments for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies, any cost-effectives analysis based on the indirect comparison (e.g., Cabazitaxel) would be biased and has important limitations that preclude drawing conclusions regarding the comparative efficacy of ^{177}Lu vipivotide tetraxetan versus Cabazitaxel. Not all evidence has been taken into account. The RWE from Cabazitaxel NHS data base should be included. In addition, CARD study which was included did not reflect current NHS practice and therefore should not be featured in the appraisal. It is not permitted and not cost effective (as previously appraised by NICE) to swich a patient to a second ARPI after a patient has progressed on a previous ARPI. A proportion of patients will develop ARPI resistance within a year and hence this may well overestimate the treatment effect of Cabazitaxel.
2	• **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The appraisal recognised the novel value of ^{177}Lu vipivotide tetraxetan in treatment of patients with mCRPC, however it has underestimated a major overall importance of this breakthrough radio molecular targeted radiotherapy in cancer treatment. The BNMS therefore urgers NICE to further negotiate the cost to find a way to implement this new game changing treatment in routine clinical NHS practice. We also recognise that the quoted list price is not a real price. We are concerned that there have been some issues with methodology of the assessment (as above). However, we also recognise this has been exceptionally difficult task in absence of any real direct comparator.
3	• **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** No. provisional recommendations are not a suitable basis for guidance to the NHS. There is a clear need for additional lines of therapy that can preserve and improve quality of life and provide meaningful survival benefits for patient with mCRPC, which 177Lu-PSMA ^{177}Lu vipivotide tetraxetan treatment can provide. BNMS is concerned that if this innovative targeted cancer treatment is not accepted for NHS patients it would remain available to those who are insured and can afford it creating a two-tear system and inequalities. Furthermore, there is unmet need for this treatment for patients who are presenting with asymptomatic bone metastases only, lymph node metastases, visceral metastases or both or all, symptomatic bone metastases with lymph node and/or visceral disease, and already undergone and/or cannot tolerate chemotherapy. The provisional recommendation not to recommend ^{177}Lu vipivotide tetraxetan would have a determinantal effect on current and further developments of molecular radiotherapy in England. This treatment has been approved in almost all developed countries and even already widely available in many developing nations (e.g.,South Africa, India etc).

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Lutetium-177 vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]

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	Due to a long-term underinvestment, nuclear medicine infrastructure in the UK would require investment and this treatment would need to be gradually adopted indeed. However, this decision would prevent any further developments, leaving England to remain placed within very few last countries in the World to approve this game changing cancer therapy. There is likely to be considerable cost saving too, as this treatment may result into less Cabazitaxel chemotherapy treatments, less hospitalisations, less severe side effects and better quality of life for patients. This preliminary recommendation, if approved, may have a broader implication preventing potential future cancer research for other tumour types (e.g., breast cancer, brain tumours/high grade glioblastomas, salivary gland tumours etc) in the UK, while most of the World continues with a progress in this field.
4	**NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.** NHS patients with mCRPC, where cancer has spread despite multiple treatments with high unmet need for new targeted treatment options to improve their outcomes, would be discriminated. They would not have any access to this treatment, while a few centres currently providing PSMA treatment privately would continue to provide it to those who can afford it, creating a two-tear system. We are also concerned that 2nd Committee (ACM2) meeting have been significantly delayed and therefore, clinical experts were not present during the entire meeting due to their prior clinical commitments and could not fully contribute to all discussions. Patients' voices have been very strong in support of PSMA treatment. Their experience with PSMA treatment particularly comparison with side effects and quality of life and outcomes clearly favouring PSMA treatment over chemotherapy should certainly be taken into account.
5	There are some inaccuracies (misinterpretation of discussion with clinical experts) in the consultation document e.g., pg 7. It should read; PSMA-ligands labelled with 68Ga and 18F are available for diagnostic purposes using PET-CT. Choline is completely different and inferior tracer to PSMA (can be labelled with 18F or 11C). It was initially used in the assessment of biochemical recurrence of prostate cancer, before PSMA-ligands were produced, but nowadays choline is only used if PSMA is not available. So, choline is not an isotope (as misrepresented in the document) than a radiotracer inferior to PSMA ligands.
6	We would also like to reiterate that 223Radium and 177Lu PSMA (^{177}Lu vipivotide tetraxetan) are entirely different in their mechanisms and hence used for different indications too. In VISION, 17.4% (145/831) of patients received prior treatment with radium-223 and 2.5% of patients received 223Ra following 177Lu-PSMA therapy. Patients with visceral disease (40-50%) are not eligible for 223Radium. Patients with nodal disease (> 3cm) are also not eligible for 223Ra. Patients with nodal disease cannot be treated with 223Ra (bone seeking agent) and patient with PSMA positive nodal disease should be treated with 177LuPSMA. Therefore, there is only a smaller proportion of patient which can potentially be treated with both (symptomatic concordant bone metastasis only). But these patients should be selected for either 223Ra or 177PSMA based on dual tracer diagnostic imaging (18F-NAF/or 99mTc bone scan and PET/SPECT-CT PSMA). There will be some proportion of patients with concordant bone lesions on both scans. However, in the context of high unmet need elsewhere this has a little impact on a broader picture of this overall NICE appraisal. There is evolving evidence that 223Ra and 177Lu-PSMA can be sequentially used with benefit in OS. In a large retrospective study, radium-223 prior 177Lu-PSMA treatment had a positive impact on OS and effect was significant in 2 subgroups: 1. 6-20 bone metastases: OS 16.4 vs 12.1; HR 1.58 (95%

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Lutetium-177 vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]

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	CI, 1.0-2.4), *P*=0.038; 2. diffuse bone involvement: OS 11.0 vs 7.1; HR 1.39 (95% CI, 1.0-1.9), *P*=0.034. WARMTH study- Ahmadzadehfar H, et al. *Eur J Nucl Med Mol Imaging*. 2021;48(12):4067-4076. Clinical data from more than 300 patients in retrospective studies suggest that sequential use of radium-223 followed by ^{177}Lu-PSMA-617 is efficacious, without any observed safety signals such as an increased risk for hematotoxicity. *Sartor O, et al. J Nucl Med. 2021;121.262240.* *Ahmadzadehfar H, et al. Oncotarget. 2017;8(33):55567-55574.* *Baumgarten J, et al. Cancers. 2022; 14(3):557.* *Groener D, et al. EJNMMI Res. 2021;11(1):61.* In summary, 223Ra should not be a comparator.

Insert extra rows as needed

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Uro-oncology Group (BUG)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	non
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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	This recommendation clearly denies deserving patients the option of treatment with Lutetium-177 vipivotide tetraxetan, within its marketing authorisation.
2	The proposal from the EAG that Lutetium Lu 177 vipivotide tetraxetan offers no benefit in overall survival versus cabazitaxel is based on a very small number of studies. NICE should consider a different methodology for the CARD study if it feels that the analysis lacks validity. It is not our practice to treat with a second ARPI after relapse on the first ARPI and therefore the control arm in the CARD study is not relevant to our practice. To assess patients progressing on an ARPI within 12 months randomized to another ARPI or cabazitaxel biases any results towards cabazitaxel.
3	The British Uro-oncology Group strongly urges NICE to review its ACD to allow appropriate patients the option of this clinically beneficial treatment.

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Lutetium-177 vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]

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

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NICE National Institute for Health and Care Excellence

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**[Prostate Cancer UK]**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**[N/A]**
Name of commentator person completing form:	[redacted]

Comment number	Comments

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	**We are concerned that this recommendation may imply that real-world evidence is not being considered in the absence of conclusive clinical trial evidence.** We recognise that the current data comparing Lutetium-177 with cabazitaxel is uncertain due to the limitations associated with the TheraP trial and the trials included in the network meta-analysis. We, therefore, urge the committee to consider the real-world evidence submitted by the company to assess the comparison between Lutetium-177 and cabazitaxel under the NICE Real-World Evidence Framework. This is because the framework was supposedly designed so that real-world evidence can be used to resolve gaps in knowledge, improve recommendations and speed up access of patients to new effective interventions such as Lutetium-177 - a novel targeted therapy agent that sets the pace for precision medicine for the treatment of metastatic hormone-relapsed prostate cancer. Moreover, during this appraisal process, several clinical experts have said that the real-world evidence submitted, is more likely to reflect clinical practice as it is more relevant to the population of men who will be receiving the treatment in the UK. Thus, it is essential that rea-world data is not ignored in this process.
2	**We are concerned that this recommendation may also imply that patients' lived experiences are not being considered in the absence of conclusive clinical trial evidence.** Lutetium has been associated with fewer 3+ side effects and an increased quality of life when compared to standard of care. This has been confirmed not only by clinicians but by patient experts too. For example, A patient who is currently receiving Lutetium-177 under the PSMAfore clinical trial described his positive experience with the treatment. To quote, "I am much stronger, and I feel much calmer and more relaxed because I am aware of the next steps and when my cycles are coming up. Also, other than the occasional dry mouth (which my doctor has given me something for), my experience with this treatment has been extraordinary as I don't really experience any other side effects". While another patient treated with Lutetium-177 has said: "As the treatment is targeted, the side-effects are minimal enabling me to continue my work and bike riding. I will be taking part in the stage 2 of the Tour de France."
3	**This recommendation also suggests that clinicians' expertise is not being taken into account in the absence of conclusive clinical trial evidence.**

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	In the absence of updated survival data, we urge the committee to consider clinicians' expertise, who administer the treatment to men with the condition and have observed the impact of Lutetium-177 in the life expectancy and quality of life of their patients first hand.
4	**We are concerned with this recommendation as there is a need for novel targeted therapies.** We disagree that Lutetium-177 is not innovative beyond what is captured in the cost- effectiveness estimates. Lutetium-177 is the first radioligand treatment of its kind for men with advanced prostate cancer. It sets the pace for precision medicine in prostate cancer and has shown to maintain quality of life and improve survival among patients with an unmet need and limited treatment options. Clinician and patient experts have provided robust evidence of the benefits and innovative aspects of the treatment throughout the appraisal process, and we urge the committee to consider their expertise in the absence of trial data.
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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

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124 City Road
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info@tackleprostate.org
www.tackleprostate.org

1st February 2023

RE: NICE Appraisal ID3840
Lutetium 177 – use in advanced Prostate Cancer

I write as the patient representative for Tackle Prostate Cancer. I was present as one of the patient experts at the recent appraisals for Lutetium 177. On the 20th January I received the confidential e-mail from NICE stating that a Final Appraisal Document (FAD) would be issued and that this would not recommend the use of Lu177 for the treatment of advanced prostate cancer in patients who had already undergone several therapies

I have had time to consider this decision. I have also been prompted to write to you having last night talked with a group of men who have advanced prostate cancer. This group meets regularly online as part of Tackle's Peer Support Programme.
The plight of many of these men who literally have no further treatment currently available to them was obvious. Some of those present would be highly likely to gain benefit from Lu 177 treatment. One man is benefiting from treatment under the EAMS scheme.

From my previous experience with NICE, I'm aware that a final decision via the FAD is difficult to overturn and that there are limited reasons for which an appeal against that FAD may be made. Before the FAD is finalised I would like to make the following comments:

1) Neither Tackle nor myself personally have the required scientific or statistical background to comment on all of the discussion that took place. However to a layperson there were obvious differences between the Company and the ERG concerning many of the elements of the appraisal.

2) Similarly, we cannot make valid comments and cost issues or health economics. Indeed we were not admitted to Part B of the committee meeting. However I firmly believe it is not the function of the patient representative to decide what the NHs can or cannot afford - that is for the politicians to sort out. it is my remit 2 ensure the best treatment is made available to all appropriate patients - however many or few the numbers of those patients maybe.

3) The FAD would appear to be directly in opposition to the views expressed by the clinical experts appointed by NICE themselves. The views of the ERG obviously 'preferred' by NICE. All of the clinical experts were of the same opinion - which from my previous experience in the past is unusual where there has not uncommonly been a degree of dissention amongst the clinical experts. Such experts are deemed to be independent of external influences from either the Company involved in the appraisal and indeed from NICE themselves.

4) Patients will find it very difficult to understand why a treatment already approved by NICE for a different cancer (neuro-endocrine tumours) is refused approval for the treatment of another cancer. This of course may be on the grounds of lack of clinical evidence of reasonable efficacy in the cancer under discussion. In order to obtain increased clinical experience with a new treatment I believe that there can be a mechanism whereby the treatment under discussion could continue to be used under close observation and data collection until sufficient evidence is available. I believe the Cancer Drugs Fund is sometimes used to provide such a mechanism? However this has already been rejected in the ACD.

5) Lu177 is already approved for treatment of advanced prostate cancer in other countries e.g. USA, Germany, Australia. in addition Lu177 is also available for use in the private sector in the UK. The treatment is obviously considered to be safe and effective. NHS patients will obviously ask why such a treatment cannot be made available to them as well - and indeed that question has already been asked of me when patients have discussed their treatment options with me in my role as providing peer support to them.

6) A further fundamental question asked of me was *"if nice do refuse to recommend Lu177 , what happens with the future use of PSMA technology and the mechanism of molecular radiotherapy"* It is not uncommon for more than one company to be involved in the same technology. The decision by NICE for Lu177 could potentially influence the progress of the use of this valuable new approach to the treatment of advanced prostate cancer.

I appreciate that decisions made by NICE are often difficult to make. the comments from patients may not always be based on hard fact and clinical research. However as the 'end users' of treatments patients do need their views to be expressed openly. That I believe is my job as a patient representative.
I am unsure whether any change or softening of the current decision by NICE is possible I do not know but I felt I should communicate my thoughts to you.

With thanks for your attention

Stephen Allen
Patient Representative
Tackle Prostate Cancer

Single Technology Appraisal

Lu vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]

Comments on the draft guidance received through the NICE website

Name	[redacted]
Role	
Comments on the DG:	

Has all of the relevant evidence been taken into account?
As you are concluding that this treatment should not be available in England whilst it is widely available in other developed countries I am not clear how you can have taken all the evidence into account. I understand that it has recently been approved for use in Canada, the latest in a series of countries where treatment for prostate cancer is being taken very seriously. You will need to be more explicit in your conclusions and recommendations to ensure that you fully evidence just why this treatment is inappropriate for use here.

Are the recommendations sound and a suitable basis for guidance to the NHS?
No they are not; if the treatment is available for those who can afford to purchase it privately then it must have some efficacy. By denying its use to the NHS you are in effect leaving NHS patients in the role of second class citizens when it comes to their health. As this treatment is one that can be used by patients who are unsuited to chemotherapy your failure to approve it means that their quality of life, albeit that it may not greatly extended, is made worse unnecessarily.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

As a male in his 70's I consider this to be discriminatory against my age and sex. Prostate cancer is among the more prevalent cancers in men and also one that may be diagnosed late in the day meaning that this type of treatment is the only one that has any efficacy. Failure to provide this on the NHS whilst it has been approved for use in England but only if you can afford to pay for it privately means that those people who have disabilities and cannot raise sufficient funds are also barred from access to this route to improve their quality of life.

Name	[redacted]
Comments on the DG:	

As a patient living with stage 4, advanced stage metastatic prostate cancer I find it appalling that we have a UK postcode lottery where men can get treatments in Scotland but not in the rest of the UK. This is not fair or equitable. I have personally benefitted from Abiraterone as a first line treatment but only because I had private medical insurance when I was diagnosed. This is typical of health care inequalities. It's my view that men should be able to access the best treatments available that help them prolong life and Abiraterone has kept me completely stable for 6 years now. I really think that you need to listen to the patients voice more when it comes to drug approval. Because I've been able to access a drug that you have refused to approve I have been able to remain economically active and contribute significantly to society and improving the lot of men diagnosed with this awful illness. However, I've also seen men be diagnosed after me and die because they have been unable to access drugs that should be available. Taking this down to a very personal level, I had one grandchild who was 3 when I was diagnosed and I didn't expect to see him become a teenager. Access to Abiraterone via my insurers means that I may have a chance of doing that and I've also seen 3 more grandchildren come into my life. Ultimately my current treatment will cease to work and if L-177 isn't approved it will limit my treatment options and therefore result in an earlier death. It will deny me the opportunity to see my grandchildren grow up. That's the real life cost of the decisions that you make. Please approve this drug and give men like me the chance to live longer with our loved ones.

Name	[redacted]
Comments on the DG:	

I have stage 4 prostate cancer and have been receiving ADT plus apalutamide. This is now failing and my PSA is increasing rapidly with a doubling time of less than a month. I am expecting to receive chemotherapy with docetaxel but understand that this will also fail in time. The knowledge that another life-extending treatment has been licensed gives me and my wife hope for more time together and the possibility of further options in the future.

It would be devastating to find that this treatment were not available to me on the grounds of cost.

I feel that NICE should give more consideration to the feelings and views of patients whose lives are directly affected by their decisions.

It is important to help men in my situation as much as possible and any extra time gives hope to their lives beyond price.

Name	[redacted]
Role	

Comments on the DG:

Has all of the relevant evidence been taken into account?

I don't think so. I am [redacted] a 74 year old performance level 1 diagnosed with mCRPC in March 2018 and being treated at UHNM Royal Stoke Hospital. I am married with 3 adult children and 7 grandchildren and have a professional working career and since retirement at age 65 are financially supported by our joint pensions. During the 5 years of treatment starting with Androgen-receptor, Docetaxel, Cabazitaxel.Radium-223 and from 2022 Abiraterone that ceased being of benefit in December 2023. UHNS Consultant referred me on 22 Nov for Lu-177 treatment but the opportunity for EAMS or other funding was lost, I know not why. I was referred to the Royal Marsden and on 16 Jan my wife and I decided to self fund a PSMA PET Ct which was positive and from then on the 22 Feb received a first infusion of LU-177, I have suffered little side effects lasting perhaps into 7 to 10 days, mainly a dry mouth and sometimes nausea but I was never sick. I ask you to imagine the effects of being advised by the NHS there are no further available treatments other than end of life care. For me with an active social life, Secretary to Staffordshire Long Distance Walkers Association, a Trustee in a voluntary social organisation and the wish to continue in reasonable health and enjoy a forward looking quality of life contributing to my family, friends and organisations. It is possible I will be unable to afford to fund more than 2, possibly 3 Lu-177 treatments.
I ask you to sanction funding for individuals in my social and health category.
Thank you
[redacted]

Are the recommendations sound and a suitable basis for guidance to the NHS? I don't think so

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Not to my knowledge

Name	[redacted]

Comments on the DG:

Has all of the relevant evidence been taken into account?

Yes - but not appreciated appropriately. It is our collective expert view (the UK Molecular Radiotherapy Consortium) that for patients with PSMA-positive mCRPC disease, Pluvicto is a superior treatment to a non-selective/targeted taxane chemotherapy agent. It is our belief that approving the use of Pluvitco will reduce the number of inpatient admissions due to sepsis when compared to Cabazitaxel, which in turn will help reduce the number of A&E admissions, in-patient bed days, etc. and thereby save overall costs.
In addition - the TheraP trial clearly demonstrates improvements in patient quality of life versus Cabazitaxel chemotherapy as well as a strong hint on overall survival benefit.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No. as detailed above and in addition, reducing hospital admissions (patients developing neutropenic sepsis / grade 3-4 diarrhoea on cabazitaxel will be cost saving. In addition - once the UK has invested in the necessary upgrades required for molecualr radiotherapy services - both diagnostic and therapeutic - the cost of treatment will be significantly reduced Using existing infrastructure, PSMA positivity can be proved for patients either by SPECT/CT, PET or gamma imaging to help access in the short to medium term. For example, 99mTc PSMA SPECT/CT imaging is more readily available than PET imaging based on currently available infrastructure.

We agree that that investment would be needed to ensure access is timely and equitable in the long-term. However, this investment is likely to be needed regardless of decisions made regarding 177Lu-PSMA-617 within its marketing authorisation, as services are already stretched and a number of disease areas (including cardiovascular disease, cancer, etc.) would benefit from increased investment in this area. Moreover, there is already evidence that people are traveling overseas to undergo PET scans. National autonomy for this service should be a goal and will require investment.
We wish to highlight that the statement indicating the most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (QALY) gained is prohibitive. We note that current ICER calculations do not take into account the benefits of not giving ineffective treatment. They also do not include costs associated with infrastructure for diagnostics.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No. The CARD trial is limited in that the true benefit of cabazitaxel vs change in ARi is over-played as a majority of patients in this trial failed on their first line ARi within 12 months - indicating that a switch in ARi would in the majority of cases be ineffective. TheraP included patients who crossed over to receive Pluvicto and yet there was still a strong hint of OS and DFS benefit in the Pluvicto arm.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No - but we do need to be acutely mindful of discrimination based upon post-code. regions of the UK outside of the South East and North west of England significantly lack in availability of diagnostic and therapeutic molecular radiotherapy facilities. There needs be an urgent acknowledgement of this going forward.

Name	[redacted]
Comments on the DG:	

I have been fortunate (so far) in that my prostatectomy last year seems to have been successful. However, I know others who have not been and therefore any support that they can get to halt the spread and give them life must be adopted! Why are patients not being listened to sufficiently to go with this drug?

Name	[redacted]
Comments on the DG:	

Has all of the relevant evidence been taken into account?

Last year I was diagnosed with terminal prostate cancer at 47. I've 4 young children 3-11 years old. From what I understand this drug has been proven to work to extend life, and with fewer adverse side effects than other treatments. For not only me, but my children and wife to have me in better health for months longer would be a massive extension which I can't put into words how much that would mean to us. Rather than arguing about the costs I would like to think as this actually works you would be looking at how to improve it to work for longer. Maybe even include some commitment from the manufacturer for more research and development as part of any price negotiation?

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? As above. While I very much appreciate budgets have to be met this is a product that works very well. This should be made available

Are the recommendations sound and a suitable basis for guidance to the NHS?

No
The phase 3 VISION trial data provides strong evidence for the use of PSMA therapy. There is an unmet need for safe and effective treatments in mCRPC. PSMA therapy is a potential 'game changer' in this group of patients. It is a precision treatment which aims to maximise treatment efficacy and reduce toxicity. Treatment is generally well tolerated with some minor treatment related side effects. PSMA molecular radiotherapy (MRT) opens up possibilities for patients who have progressed through or who are ineligible for other therapeutic options

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? No

Has all of the relevant evidence been taken into account?
Last year I was diagnosed with terminal prostate cancer at 47. I've 4 young children 3-11 years old. From what I understand this drug has been proven to work to extend life, and with fewer adverse side effects than other treatments. For not only me, but my children and wife to have me in better health for months longer would be a massive extension which I can't put into words how much that would mean to us. Rather than arguing about the costs I would like to think as this actually works you would be looking at how to improve it to work for longer. Maybe even include some commitment from the manufacturer for more research and development as part of any price negotiation?

Are the recommendations sound and a suitable basis for guidance to the NHS?

Approving one treatment that is a lot cheaper, but much less effective rather than one that is much more expensive, but does a far
but does a far better job is flawed advise. A few months extra doesn't sound much, but when you don't have long to live with your loved ones it's a massive amount of time. Please help us.

Name	[redacted]
Conflict	
Notes	
Comments on the DG:	

It is a concern that the spc does not satisfy UK regulations regarding patient dosimetry and that this does not seem to have been considered as yet.

The UK Ionising Radiation (Medical Exposure) Regulations 2017 states that:

Optimisation
(2) In relation to all radiotherapeutic exposures the practitioner must ensure that exposures of
target volumes are individually planned and their delivery appropriately verified taking into

account that doses to non-target volumes and tissues must be as low as reasonably practicable and
consistent with the intended radiotherapeutic purpose of the exposure.

where

“radiotherapeutic” means pertaining to radiotherapy, including nuclear medicine for therapeutic purposes;

The capability to image the biodistribution of both Lu-177 and Ra-223 is unmatched by taxane-based chemotherapy or anti-androgens. Post-therapy imaging and radiation dosimetry of Pluvicto allows patient-specific dosimetry that would inform treatment

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?
Has all of the relevant evidence been taken into account?
No. Radioactive drugs are a form of radiotherapy. Treatment outcomes, in terms of radiological response and toxicity, are dependent on the radiation doses delivered to disease and to organs-at-risk, as is the case for external beam radiotherapy or brachytherapy.

The results of the VISION trial show that the drug was ineffective for 50% of patients. In 5% of cases treatment led to death, either directly from irradiation or from radiation related SAEs. The range of responses seen is consistent with the reported range of radiation doses delivered in numerous publications.

Although radiation dosimetry was performed at selected sites within the VISION trial, this was not reported and has not been taken into account. As SAEs may occur following more than one administration, these may be preventable if the initial dose profile is known. Whether SAEs occurred after more than one administration was not reported but should be taken into account.

Patient-specific radiation dosimetry is a requirement of the Ionising Radiation (Medical Exposure) Regulations 2017 (section 12(2), explicitly including for nuclear medicine purposes. Approval of the drug without allowance for post therapy imaging and radiation dosimetry may leave centres and practitioners open to litigation.

Are the recommendations sound and a suitable basis for guidance to the NHS?
Difficult to be certain, given the complexities of the analysis, the redaction and the lack of cost information. This new technology certainly offers advantages over conventional chemo.

Name	[redacted]
Comments on the DG:	

I AM 68 AND WAS DIAGNOSED WITH PROSTATE CANCER (INCURABLE BUT TREATABLE) IN LATE 2021. APART FROM THE CANCER I AM FORTUNATE IN NOT HAVING ANY OTHER MAJOR HEALTH CONDITIONS. I AM EXTREMELY MOTIVATED TO LIVE A GOOD QUALITY LIFE AND MAKE A POSITION CONTRIBUTION TO SOCIETY AS LONG AS POSSIBLE. THROUGHOUT MY LIFE I HAVE EXERCISED REGULARLY AND FOLLOWED A HEALTHY DIET. I NOW EXERCISE ALMOST EVERY DAY (CYCLING, SWIMMING, RESISTANCE TRAINING AND WALKING) AND CONSIDER MYSELF FIT FOR MY AGE. MY BMI IS CURRENTLY 22 AND MY BODY FAT IS C.17%.
I AM CURRENTLY RECEIVING HORMONE THERAPY (ZOLADEX) WHICH IS PROVING EFFECTIVE SO FAR AS MY PSA IS ONLY 0.006, WHICH IS VERY ENCOURAGING. HOWEVER, I AM AWARE THAT EVENTUALLY IT WILL LOSE ITS EFFICACY AND FURTHER TREATMENTS WILL BE REQUIRED WHICH MAY OR MAY NOT PROVE EFFECTIVE. THE REALISATION THAT THESE OTHER TREATMENTS EXIST IS REASSURING AND A MAJOR FACTOR FOR MY GOOD MENTAL HEALTH AND IN HELPING ME MAINTAIN A POSITIVE OUTLOOK. WHILE I DO NOT DWELL ON MY ILLNESS, IT IS IMPOSSIBLE NOT TO THINK OF IT ON OCCASION EACH DAY, AND I LIVE IN HOPE FOR ADVANCES IN TREATMENTS THAT WILL SIGNIFICANTLY PROLONG MY LIFE. EACH TIME I HEAR OF A NEW DRUG THAT MAY PROVE MORE EFFECTIVE AGAINST MY ILLNESS IT FUELS MY HOPES SINCE THE MORE DRUGS THE NHS HAS IN ITS ARMOURY THE GREATER THE CHANCES THAT SOME OF THEM MAY PROVE BENEFICIAL FOR ME. I WOULD INCLUDE

PLUVICTO IN THAT CATEGORY, AND TO HEAR THAT IT WAS INITIALLY REJECTED BY NICE DESPITE BEING USED IN OTHER COUNTRIES IS EXTREMELY DISPIRITING AND DEMOTIVATING. AS MY CANCER IS NOT CURRENTLY IMPACTING ME PHYSICALLY MY BATTLE WITH IT IS ESSENTIALLY MENTAL AT THE MOMENT SO ANY GOOD NEWS INCREASES MY FORTITUDE TO KEEP LIVING WELL AND TO CONTINUE TO MAKE A POSITIVE IMPACT ON SOCIETY. I REMAIN OPTIMISTIC THAT A CURE WILL BE FOUND IN MY LIFETIME SO MY OBJECTIVE IS TO DO ALL I CAN TO REMAIN ALIVE UNTIL THEN SO THAT HOPEFULLY MY SENTENCE ON DEATH ROW CAN BE COMMUTED. I SEE INNOVATIVE TREATMENTS SUCH AS PLUVICTO AS A KEY ELEMENT IN HELPING ME ACHIEVE THIS GOAL.

Has all of the relevant evidence been taken into account?
I DON'T BELIEVE THE VIEWS OF PROSTATE CANCER SUFFERERS HAVE BEEN TAKEN INTO ACCOUNT SUFFICIENTLY. AS A SUFFERER MYSELF I HAVE INCLUDED MY VIEWS IN THE 'COMMENT ON THE DOCUMENT' SECTION.

Are the recommendations sound and a suitable basis for guidance to the NHS?

NO. THE REASON FOR THIS IS THAT THE EVIDENCE ON WHICH THEY ARE BASED DOES NOT TAKE SUFFICIENT ACCOUNT OF THE VIEWS OF CANCER SUFFEFERS.

Name	[redacted]
Comments on the DG:	

Has all of the relevant evidence been taken into account?

We have two major concerns in relation to this appraisal. Firstly, relating to NICE's treatment of real-world evidence (RWE) and secondly with regards to the impact of expert clinical and patient experience.

RWE has been described in the NICE Strategy 2021 - 2026 as an important resource for resolving evidence gaps, for example in providing indirect comparators alongside data from clinical trial arms. Whilst the value of RWE lies in its very derivation from routine clinical practice there are challenges inherent in its inclusion in formal appraisals which NICE appears yet to have fully resolved. In the case of the Pluvicto TA, based upon stated views of expert clinicians that Cabazitaxel would not be used instead of Pluvicto, we do not agree in any case that Cabazitaxel should be used as a comparator. Given the level of uncertainty described by the NICE evaluation, we believe that the NICE committee should place more emphasis on evidence that was presented by patients and clinicians.

NICE has committed to exploring new was of engaging and using patient experience to inform the evidence base for guidance development. This commitment is welcome, but over and above ways of engaging patients, what is needed is a commitment to demonstrable patient involvement in decision making. Whilst accepting that NICE has to strike a balance between considering health economic evaluation and expert clinical and patient evidence, we do not believe that this balance is currently right. It is unclear what impact, if any, evidence presented by patient and clinical experts has had on the bottom line in the case of this particular appraisal.

Patient and clinician views in the case of Pluvicto were overwhelming strongly in favour of a favourable outcome. This negative decision is a substantial blow to patients whose length and quality of life could be meaningfully improved by this treatment.

Name	[redacted]
Comments on the DG:	

Has all of the relevant evidence been taken into account?

NICE has said they will consider real-life evidence in these matters and I do not believe they have done so. This treatment will make a huge difference to patients that have Stage 4 Metastatic prostate cancer due to the limited treatment options currently available. It has been shown to be effective and will make a real difference in men's lives. If you do not approve this drug you are condemning men to a slow painful death due to a lack of other treatment options. This is agony for their families and when you have the power to give them more time together or prevent this altogether, I believe you have a duty to do so.

It is not fun, spending each Christmas worrying if it may be the last for your family member and knowing that there is a drug available that has been denied after limited clinical testing and based upon financial costs is heart-breaking.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?
Given this is a relatively new drug, there are only so many effectiveness studies that can be done within a clinical setting. This drug needs a chance to be utilised within the real world, only then will the true benefits be realised.

My father has been on hormone therapy for 26 years, having recently moved onto Enzalutamide. This has never been discovered in a clinical testing setting to date. Such a practice based observation of interesting which may help treat other individuals would have been lost if stuck to a clinical testing based environement.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I do not believe that they are suitable as they do not take into account real life evidence and a longitudinal study on effectiveness.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Name	[redacted]
Notes	
Comments on the DG: As a person who has aggressive advanced prostate cancer I wanted to comment on your report.	

As a patient who has been deemed unfit for taxane medication, I have limited options for treatment beyond the Enzalutamide I am now taking. This has been a marvellous medication that has kept my cancer in check and my PSA at normal levels for close on two years now, allowing me to continue to work, live a normal life and have precious time with my loved ones. I have been so very grateful that this medication was made available. Thank you for that! I am all too conscious that it's efficacy will wane though in the not too distant future, which will then leave me with very few options before my cancer progresses even further and my quality of life will quickly deteriorate. I have watched with great excitement the progression of the LuPSMA trials and the wonderful results it has produced allowing men in my position a decent sized ray of hope. It is one of the best new treatments in a long time for cancer. As noted in your report, the use of it early on in treatment could also be very beneficial, meaning less of a load for the NHS in appointments, and use of other treatments. Nipping it in the bud so to speak. I feel I have so much more to give in both my work and family life, as do so many men in my position, many who are contracting this disease at earlier and earlier ages, still with young families.
I implore you to reconsider making this available to men in my position. I understand the cost is high, but weighed up against the contributions of thousands of men being able to continue working, living, loving, putting into society and the benefits in the long run to the NHS with a lessened load on other treatment plans should surely be worthy of consideration, and to be at the forefront of using state of the art medications for a disease that at present affects 1 in 8 men, similar statistics to women with breast cancer, can only be a wonderful, progressive and compassionate decision.

Has all of the relevant evidence been taken into account?
Last year I was diagnosed with terminal prostate cancer at 47. I've 4 young children 3-11 years old. From what I understand this drug has been proven to work to extend life, and with fewer adverse side effects than other treatments. For not only me, but my children and wife to have me in better health for months longer would be a massive extension which I can't put into words how much that would mean to us. Rather than arguing about the costs I would like to think as this actually works you would be looking at how to improve it to work for longer. Maybe even include some commitment from the manufacturer for more research and development as part of any price negotiation?

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
As above. While I very much appreciate budgets have to be met this is a product that works very well. This should be made available across the whole country rather than postcode lottery.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Approving one treatment that is a lot cheaper, but much less effective rather than one that is much more expensive, but does a far better job is flawed advise. A few months extra doesn't sound much, but when you don't have long to live with your loved ones it's a massive amount of time. Please help us.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Name	[redacted]

Comments on the DG:

Has all of the relevant evidence been taken into account?
I am a patient who has benefited from this treatment. I was diagnosed in 2017 with MCRPC and following disease progression had recently run out of NHS treatments. All other options including taxane chemotherapy had stopped working. I have had all available alternative NHS treatments. I had the Lutetium 177 treatment under the EAMS scheme and had my first infusion on Thursday 16th February. In the weeks prior to this treatment I felt so unwell and could hardly walk and was frankly beginning to give up hope. I was so weak I was not sure I would be able to get to the hospital. Following the Lutetium 177 treatment my pain has lessened considerably, to almost none existent and I am able to walk good distances again. I feel so much better and its incredible this is only 1 week after my 1st treatment! I know its early days and I don't know how long the treatment will last but I am so grateful that I have benefited from it so far. I could quite simply not afford it if I didn't get in on the EAMS scheme. I believe it is imperative that this new, revolutionary treatment is afforded to all men who might find themselves in the same position as me. I genuinely and honestly believe it has saved my life. I am not sure how long I would have lasted if I hadn't had it. I am only 59 and have a large family. I believe this treatment has given me invaluable additional time with them.

Name	[redacted]

Comments on the DG:

Has all of the relevant evidence been taken into account?
I am an individual, who has so far been cured of Locally Advanced Prostate Cancer. However, on the aggresiveness scale I am 9/10, so there is a real chance of the cancer returning and going metastatic. I want to ensure that there is a pipeline of effective drugs with fewer side effects if this is the case.

Approval of this drug will have a significant impact already for me. Each six months I have a blood test to determine if my cancer continues in remission.

It is like playing Russian Roulette! If I know this drug is approved my stress and anxiety levels will be much reduced.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

How would I judge cost effectiveness of my life being extended!

Name	[redacted]
Notes	

Comments on the DG:

Has all of the relevant evidence been taken into account?

I don't believe that the full impacts of withholding this drug have been explored with those who will need it.
I believe that the cost-benefit of the extra time this drug will provide is more than enough to justify its use.
Most of the recipients will have paid into the UK Tax system for many years so surely, they should be given every bit of help in their time of need. What is the price of life/time with loved ones?

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No - The drug should be available to those who need it.
Impacts on potential recipients have not been thoroughly explored.
As someone diagnosed with Prostate cancer, I want every chance to live as long as possible and think that any drug that will help should be available.
I've paid into the UK Tax system since I was 16 years old so why should my life expectancy be impacted by the cost of this drug?

Are the recommendations sound and a suitable basis for guidance to the NHS?

No - The drug should be made available if the physician deems it suitable to prolong life.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

If there are similarly priced drugs available for other illnesses that don't impact men generally in their later years then yes, there is discrimination here.

Name	[redacted]
Comments on the DG:	
Has all of the relevant evidence been taken into account? As a person who has aggressive advanced prostate cancer I wanted to comment on your report. As a patient who has been deemed unfit for taxane medication, I have limited options for treatment beyond the Enzalutamide I am now taking. This has been a marvellous medication that has kept my cancer in check and my PSA at normal levels for close on two years now, allowing me to continue to work, live a normal life and have precious time with my loved ones. I have been so very grateful that this medication was made available. Thank you for that! I am all too conscious that it's efficacy will wane though in the not too distant future, which will then leave me with very few options before my cancer progresses even further and my quality of life will quickly deteriorate. I have watched with great excitement the progression of the LuPSMA trials and the wonderful results it has produced allowing men in my position a decent sized ray of hope. It is one of the best new treatments in a long time for cancer. As noted in your report, the use of it early on in treatment could also be very beneficial, meaning less of a load for the NHS in appointments, and use of other treatments. Nipping it in the bud so to speak. I feel I have so much more to give in both my work and family life, as do so many men in my position, many who are contracting this disease at earlier and earlier ages, still with young families. I implore you to reconsider making this available to men in my position. I understand the cost is high, but weighed up against the contributions of thousands of men being able to continue working, living, loving, putting into society and the benefits in the long run to the NHS with a lessened load on other treatment plans should surely be worthy of consideration, and to be at the forefront of using state of the art medications for a disease that at present affects 1 in 8 men, similar statistics to women with breast cancer, can only be a wonderful, progressive and compassionate decision.	

^{177}Lu vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]

Addendum: EAG comments on the company's response to the Appraisal Consultation 2

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1 Introduction

In February 2023, the National Institute for Health and Care Excellence (NICE) issued a negative Appraisal Consultation Document 2 (ACD2) for ^{177}Lu vipivotide tetraxetan for the treatment of prostate-specific membrane antigen (PSMA)-positive hormone-relapsed metastatic prostate cancer in adults after taxane-based chemotherapy and an anti-androgen or when taxanes are 'medically unsuitable'.[1] The ACD2 states that the most likely cost-effectiveness estimates for ^{177}Lu vipivotide tetraxetan compared to standard of care (SOC) and to cabazitaxel are much higher than what NICE normally considers an acceptable use of NHS resources. It also states that radium-223 dichloride may be a comparator for a subgroup of people, but it could not be considered because no evidence was submitted for this comparison.

In June 2023, the company submitted a response to ACD2.[2] The company's response includes a written document and an updated version of the base case model which includes some of the Appraisal Committee's preferred assumptions. The company's response document provides additional discussion around the following six key points: (i) the estimation of the relative effect of ^{177}Lu vipivotide tetraxetan vs. cabazitaxel; (ii) the use the real-world evidence (RWE) overall survival (OS) to inform the absolute efficacy of cabazitaxel with a hazard ratio (HR) derived from the unanchored matching-adjusted indirect comparison (MAIC) to estimate survival for ^{177}Lu vipivotide tetraxetan; (iii) the exclusion of radium-223 as a comparator; (iv) the generalisability of the base case analysis to patients medically unsuitable for taxanes; (v) the use of treatment-dependent utility values; and (vi) the PSMA testing costs.

Additional scenario analyses are presented around several of these issues. The company has not proposed a new Patient Access Scheme (PAS) discount for ^{177}Lu vipivotide tetraxetan since their response to the Appraisal Consultation Document 1 (ACD1) ([redacted], discounted cost per pack = [redacted]).[3]

This External Assessment Group (EAG) addendum provides a commentary on the company's ACD2 response[2] and should be read in conjunction with the EAG report,[4] the EAG's response to technical engagement (TE),[5] and the EAG's comments on the company's ACD1 response.[6] Section 2 provides a summary of the company's response to the ACD2 and the EAG's critique of these points. Section 3 presents the results of the company's revised base case model. Section 4 presents additional exploratory analyses undertaken by the EAG.

2 Summary of the company's response to the ACD2 and EAG critique

This EAG addendum is structured around the six issues discussed in the company's response to the ACD2 which are detailed in Sections 2.1 to 2.6. Each section summarises the company's position and also includes the EAG's opinion of the new data and/or assumptions.

2.1 Issue 1: The estimation of the relative effect between ^{177}Lu vipivotide tetraxetan and cabazitaxel

The company confirms that the timing of prior androgen receptor pathway inhibitor (ARPI) progression represents an important confounder of the relative treatment effect in any indirect comparisons and conducts two additional indirect treatment comparison (ITC) analyses to estimate the relative treatment effect for OS and radiographic progression-free survival (rPFS) between ^{177}Lu vipivotide tetraxetan and cabazitaxel:

- a Bucher ITC based on the CARD trial and a subgroup of patients from the VISION trial who had ARPI prescribed as part of standard of care (SOC) and had progressed within 12 months of receipt of a prior ARPI (the ARPI and progressed ≤12 months of receipt of a prior ARPI subgroup);
- an unanchored MAIC based on the cabazitaxel arm from the CARD trial and a subgroup of patients from the ^{177}Lu vipivotide tetraxetan arm of the VISION trial who had an ARPI prescribed as part of SOC (the ARPI-subgroup).

A Bucher ITC

The company states that using the ARPI and progressed ≤12 months of receipt of a prior ARPI subgroup resolves differences between the VISION and CARD trial due to this important treatment effect modifier. For OS, this subgroup population includes [redacted] in the ^{177}Lu vipivotide tetraxetan arm and [redacted] in the SOC arm, which presents [redacted] of patients included in the ARPI-subgroup of the VISION trial. For rPFS, the subgroup population includes [redacted] patients in the ^{177}Lu vipivotide tetraxetan arm and [redacted] in the SOC arm, which presents [redacted] of patients included in the ARPI-subgroup of the VISION trial.

The results of a Bucher ITC for OS and rPFS are presented in **Table *1***. The company lists the following limitations of this analysis: (i) breaks randomisation as time to progression on an ARPI was not a stratification factor in the VISION trial; (ii) adjusting for differences in patient characteristics across the VISION treatment arms was not feasible due to small sample size; (iii) the treatment effect derived from VISION and CARD are not comparable due to the control arm in the VISION trial ARPI-subgroup and the control arm in the CARD trial being heterogeneous in the treatment intentions. The company states that "*Patients in VISION were prescribed ARPI as part of SOC based on clinical judgement, likely where there may be an expectation of additional clinical benefit*." and "*patients receiving a second ARPI was mandated in the control arm of CARD*."

The EAG notes that the 99.2% confidence interval (CI) was used instead of the 95% CI for deriving the treatment effect for rPFS and OS for the ARPI and progressed ≤12 months of receipt of a prior ARPI subgroup. In response to EAG questions post-ACD2,[7] the company clarifies that the choice of 99.2% in this subgroup analysis was "*aligned to the pre-specified primary analysis of rPFS in the VISION trial*", however, "*this was erroneously applied to the subgroup analysis of overall survival (OS) presented in*

the company's second ACD response." The company confirms that the 99.2% CIs were converted to 95% CIs prior to use in the Bucher ITC.

An unanchored MAIC

The company adjusted for six variables (proportion of patients with ECOG performance status of 0 to 1, presence of liver or lung metastases, presence of bone metastases, proportion of patients who had received docetaxel before ARPI, median age and proportion of patients with Gleason score of 8 to 10) in the unanchored MAIC analysis. The variables were identified via a systematic literature review (SLR) of prognostic variables and confirmed through clinical expert opinion.[8, 9] The results of the unanchored MAIC for OS and rPFS are also presented in **Table *1***.

The company uses the HR from the unanchored MAIC (after weighting) for OS in the revised base case given that it has the greater sample sizes and smaller confidence intervals as compared to the Bucher ITC. The company uses the HR from the EAG-preferred network meta-analysis (NMA) (see **Table *1***) for rPFS in the revised base case given the similarity in HRs for rPFS from various methods. The HR for rPFS from the unanchored MAIC was applied in a scenario analysis.

Table 1: Results of the company's Bucher ITC and unanchored MAIC, and EAG ACM2 NMA for OS and rPFS

	Bucher ITC (95% CI)	MAIC before weighting (95% CI)	MAIC after weighting (95% CI)	EAG ACM2 NMA (95% CrI)
OS	[redacted]	[redacted]	[redacted]	1.00 (0.44, 2.24)
rPFS	[redacted]	[redacted]	[redacted]	0.77 (0.47, 1.20)

Abbreviations: OS: overall survival; rPFS: radiographic progression-free survival; CI: confidence interval; CrI: credible interval; ITC: indirect treatment comparison; MAIC: matching-adjusted indirect comparison; NMA: network meta-analysis.

EAG critique: The company's Bucher ITC aims to adjust for the difference in the timing of prior ARPI progression between the CARD and VISION trial. The EAG is unclear how the subgroup of patients who had progressed within 12 months of receipt of a prior ARPI were identified from the VISION trial; whether this data was collected as a part of the patient baseline characteristics; and for patients who had more than one ARPIs, how progression within 12 months of receipt of a prior ARPI was defined. In response to EAG questions post-ACD2,[7] the company states that "*The exact derivation of time to progression on a prior androgen receptor pathway inhibitor (ARPI) in the VISION trial is being sourced by the company's statistics team, and will be provided as soon as it is available*." The EAG has not received further responses from the company at the time of writing this addendum.

The EAG notes that the Bucher ITC is equivalent to a fixed effect NMA which assumes that there is no heterogeneity between the included studies. The EAG also notes that the relative treatment effect obtained from the company's Bucher ITC represents the relative treatment effect between ^{177}Lu vipivotide tetraxetan and cabazitaxel in the subgroup of patients who had ARPI prescribed as part of SOC and had progressed within 12 months of receipt of a prior ARPI. The point estimate of the relative treatment effect for ^{177}Lu vipivotide tetraxetan versus SOC is more in favour for ^{177}Lu vipivotide tetraxetan in this subgroup compared to the treatment effect in the ARPI-subgroup (OS: [redacted] vs. [redacted]; rPFS: [redacted] vs. [redacted]).

The company argues that there is an important difference between treatment with an ARPI as part of SOC in the VISION trial and as part of the control arm in the CARD trial: ARPI as part of SOC was prescribed based on clinical judgement in the VISION trial but was mandated in the control arm in the CARD trial). The EAG notes that [redacted] as stated in the clinical study report of the VISION trial.[10]

The company states that the covariates selection in the unanchored MAIC was based on an SRL of prognostic variables and confirmed through clinical expert opinion. The EAG notes that the SRL identified 20 variables having strong/significant association with OS and the top five variables were Prostate Specific Antigen (PSA; baseline/response/change), ECOG, alkaline phosphatase (baseline/change/total), haemoglobin level, and lactate dehydrogenase (baseline/change). The company's clinical expert advisory board meeting report shows that [redacted].[9] The EAG highlights that there are noticeable differences in baseline PSA, alkaline phosphatase, and lactate dehydrogenase between the two intervention arms included in the unanchored MAIC and the company's unanchored MAIC results are subject to substantial uncertainty without adjusting for these important prognostic factors.

In response to EAG questions post-ACD2,[7] the company states that the weighted Cox regression model was used in the unanchored MAIC. However, the EAG is not clear whether a robust standard error was obtained to calculate the 95% CI.

In response to ACD1,[3] the company updated the NMA for OS with inverse probability of censoring weighting (IPCW)-adjusted VISION data, as preferred by the Appraisal Committee. The company also updated the NMA for rPFS using the interval imputed VISION data. The NICE ACD2 states that "*The*

committee agreed that accounting for any bias introduced in VISION and withdrawal rates was appropriate." The EAG notes that the VISION data used in the Bucher ITC and unanchored MAIC were not IPCW-adjusted or interval imputed, the impact of omitting these adjustments is unclear. The EAG's NMA presented in **Table *1*** used IPCW-adjusted VISION data for OS and interval imputed VISION data for rPFS which were consistent with the analyses presented in the ACD1.

In summary, the EAG cautions the interpretation of the results from the Bucher ITC and unanchored MAIC due to the following limitations associated with these analyses:

- unadjusted VISION data were used in these analyses;
- exclusion of the TheraP trial, not in line with the Committee's preference;
- the Bucher ITC is equivalent to a fixed effect NMA assuming no heterogeneity between the CARD trial and the subgroup of the ARPI and progressed ≤12 months of receipt of a prior ARPI in the VISION trial;
- the lack of adjusting for certain important covariates in the unanchored MAIC.

2.2 Issue 2: Use the RWE OS to inform the absolute efficacy of cabazitaxel with a HR derived from the unanchored MAIC to estimate survival for ^{177}Lu vipivotide tetraxetan

The company's revised base case adopts the use of RWE OS data to inform the absolute efficacy of cabazitaxel. The HR derived from the unanchored MAIC has been applied to the cabazitaxel RWE OS curve to estimate the OS for ^{177}Lu vipivotide tetraxetan in the model. A scenario analysis has also been presented using the HR from the EAG's preferred NMA for completeness. The company also states that "*the re-analysis of RWE PSW is underway which is anticipated to provide further evidence for relative efficacy*."

EAG critique: The use of RWE OS data is in line with the Committee's preferred analysis. Due to the substantial uncertainty associated with the unanchored MAIC, the EAG also presents a scenario analysis using the HR from the Bucher ITC in addition to presenting a scenario using the EAG's preferred NMA.

2.3 Issue 3: The exclusion of radium-223 as a comparator

The company reiterates that only a small number of patients in clinical practice would be anticipated to be considered for treatment with radium-223 and ^{177}Lu vipivotide tetraxetan. The company also reiterates that a robust comparison in the population of interest is not feasible due to heterogeneity between the CARD and ALSYMPCA trials, and the ALSYMPCA trial only reporting the result for OS not for rPFS. The company states that they have not been able to source alternative data to inform a robust indirect treatment comparison between ^{177}Lu vipivotide tetraxetan and radium-223.

The company highlights that in the recent NICE appraisal of olaparib for adults with hormone-relapsed metastatic prostate cancer with BRCA1 or BRCA2 mutations that have progressed after an ARPI, the EAG accepted the exclusion of radium-223 as a comparator based on the comparison was considered infeasible.[11]

The company concludes that they "*maintain that radium-223 cannot be included as a comparator in this submission, and that its exclusion does not represent a major source of uncertainty*."

EAG critique: The EAG highlights that the company did not provide any new evidence/justifications for the exclusion of radium-223 apart from pointing out that the EAG in TA887 accepted the exclusion of radium-223 in a similar indication.

The EAG notes that the size of the population for which radium-223 would be a comparator for ^{177}Lu vipivotide tetraxetan is unclear. The ACD2 states that "*One expert estimated that about 30% of people who could have lutetium-177 may have bone metastases alone, but 10% to 15% would have isolated symptomatic bone metastases (as needed for treatment with radium-223).*"[1] and this estimate is much higher than the company's estimate, using the RWE data, that [redacted] of patients with metastatic castration-resistant prostate cancer (mCRPC) would be eligible for radium-223 post-docetaxel and ARPI.

The EAG maintains its view that radium-223 should be a comparator for the subgroup of patients with bone metastases who do not have visceral metastases in the post-ARPI and taxane setting and in the post-ARPI setting where docetaxel is contraindicated or unsuitable. The EAG's critique around this issue can be found in the original EAG report (Section 2.2) and TE response (Table 1, key issue 2).[4, 5] As the company has not presented any new evidence/justifications around this issue, the EAG's view remains unchanged.

2.4 Issue 4: Generalisability of the base case analysis to patients medically unsuitable for taxanes

The Appraisal Committee acknowledged a likely worse prognosis in patients who are medically unsuitable for taxanes and *"agreed that scenario analyses using the same relative treatment effect as for the wider population but with a higher baseline risk, and so a worse overall survival would be useful*".

The company reiterates that introducing ^{177}Lu vipivotide tetraxetan would address the high unmet need for patients medically unsuitable for taxanes as they face limited treatment options. The company argues that "*the current poor prognosis for patients not medically suitable for taxanes is a result of the lack of effective treatment options, and therefore may not be a good predictor of the ability of such patients to*

respond to treatment with ^{177}Lu vipivotide tetraxetan." The company also argues that, "*failure of prior taxane therapy is an important prognostic factor, and thus patients medically unsuitable for taxanes may in fact have an improved comparative prognosis on ^{177}Lu vipivotide tetraxetan than patients who have received and failed treatment with docetaxel.*" and provides four studies which support the claim of better outcomes in patients receiving ^{177}Lu vipivotide tetraxetan who have not previously received taxanes.[12-15]

The company presented two scenario analyses for the comparison between ^{177}Lu vipivotide tetraxetan and SOC, where they adjust the OS and rPFS estimates for both ^{177}Lu vipivotide tetraxetan and SOC treatment groups using data from Ahmadzadehfar *et al.* (2020),[12] where the impact of prior therapies on overall survival was evaluated in mCRPC patients who received ^{177}Lu vipivotide tetraxetan (WARMTH study). This retrospective study found that patients without a history of prior chemotherapy at the time of starting ^{177}Lu vipivotide tetraxetan had better overall survival than those with a history of prior chemotherapy, which the EAG notes is the opposite to the expectation expressed by the Committee in ACD2. The company applied the estimated HRs from univariate and multivariate analyses from patients who had history of receiving previous chemotherapy in comparison to patients who received no chemotherapy from the WARMTH study to both OS and rPFS estimates for both ^{177}Lu vipivotide tetraxetan and SOC group.

EAG critique: The EAG notes that the company does not provide the analysis as preferred by the Committee, instead the company presented additional evidence on the treatment effect of ^{177}Lu vipivotide tetraxetan for patients who have not previously received taxanes. The company states that they use the HR "*between the subgroups having received prior taxane therapy and those having no prior history of taxane-based chemotherapy*" from Ahmadzadehfar *et al.* (2021).[12] The EAG notes that the subgroup "*having no prior history of taxane-based chemotherapy*" refers to patients who avoided chemotherapy in Ahmadzadehfar *et al.* (2021) study and it is not clear what were the reasons behind avoiding chemotherapy. The authors of Ahmadzadehfar *et al.* (2021) divided these patients into those who avoided it despite lacking contraindications (N=83) and those who were contraindicated (N=19), but did not distinguish between these two groups in the comparison of with versus without prior chemotherapy. Another important limitation of the study, highlighted by the authors themselves, is its retrospective nature and the inherent potential for lag-time bias, where it is unclear if patients who have not received previous chemotherapy were in an earlier timepoint of their disease progression, in comparison to those who have received previous treatment.

The EAG considers that the additional analyses submitted by the company should be considered with extreme caution due to the potential for lag-time bias and the retrospective nature of the WARMTH study used to adjust for OS and PFS. The EAG believes that there is considerable uncertainty of the

applicability of the cost-effectiveness estimates obtained for ^{177}Lu vipivotide tetraxetan to those patients who are medically unsuitable for taxanes due to paucity of clinical data on effectiveness for this group. The EAG's view of the available clinical evidence and uncertainty around the relative treatment effects of ^{177}Lu vipivotide tetraxetan in this subgroup therefore remains unchanged. The EAG's full critique around this issue is presented in the original EAG report (Section 4.3.4, issue 2), TE response (Table 1, key issue 1) and ACD 1 response (Section 2.3, issue 3).[4-6]

2.5 Issue 5: The use of treatment-dependent utility

Section 3.14 of the NICE ACD2 document,[1] in face of the different analyses presented by the company and the EAG during the appraisal, states that the Appraisal Committee *"acknowledged that it preferred to have treatment independent utilities with adverse event decrements including grade 2 adverse events."* The Committee's preference was based on feedback from clinical experts who affirmed that utility would be expected to be lower at baseline with cabazitaxel due to delays in treatment with chemotherapy because of patient preferences that can result in the patient's condition deteriorating, or because utility can be affected by the anxiety of having a similar chemotherapy again. A clinical expert also stated during the committee meeting that "*persistent grade 2 side effects, such as fatigue or neuropathy, can have a debilitating effect on people.*" The NICE ACD2 also states that "*The committee usually prefers treatment-independent utility values. But it accepted that using treatment-dependent utility values for decision making may be appropriate in this appraisal because grade 2 adverse events had not been included. But it thought that scenarios including treatment-dependent and treatment-independent utility values would be helpful.*"[1]

In its response to the ACD2 document,[2] the company maintains its position to use treatment-dependent utility values as part of their base case analysis, based on the view that treatment-independent utilities are "*unlikely to fully account for patients' experience of treatment, in particular with cabazitaxel.*" The approach presented by the company as the new base case corresponds to the EAG exploratory analysis 3 presented at the technical engagement stage (TE-EA3), which includes treatment-dependent utility values using the company's original utility analysis, excludes additional utility decrements for adverse events (AEs) and symptomatic skeletal events (SSEs), and applies for cabazitaxel pre- and post-progression health states the average of the utility values for ^{177}Lu vipivotide tetraxetan and SOC.

In order to address the Appraisal Committee's considerations regarding the utility values, the company also presents three additional scenario analyses for the comparison between ^{177}Lu vipivotide tetraxetan and cabazitaxel, which include in all of them the use of treatment-independent utility values for all treatment groups from the company's original utility analysis with the exception of pre-progression health state for cabazitaxel, where the average of the utility values for ^{177}Lu vipivotide tetraxetan and

SOC was applied. In addition, each of the analyses explored different assumptions for neuropathy and fatigue/asthenia AEs:

- Scenario 5: only grade ⩾3 AEs were included for ^{177}Lu vipivotide tetraxetan and cabazitaxel, but neuropathy and fatigue/asthenia AEs are assumed to last for the whole duration of treatment for patients receiving cabazitaxel (5.06 months). The company includes the justification for this approach on being aligned with treatment duration from CARD and from clinical and patient feedback in ACD2;
- Scenario 6: use of all-grade (≥1) incidence of neuropathy and fatigue/asthenia AEs for ^{177}Lu vipivotide tetraxetan and cabazitaxel, whilst the duration of all AEs was assumed to be 1 month (in line with the company's original assumptions). The company assumed the same utility decrement values for all AE grades;
- Scenario 7: use of all-grade (≥1) incidence of neuropathy and fatigue/asthenia for ^{177}Lu vipivotide tetraxetan and cabazitaxel, and the AE duration for these events was assumed to be 5.06 months for cabazitaxel patients.

The AE incidences for fatigue, asthenia and neuropathy applied in previous iterations of the appraisal and in the company's ACD2 response updated base case and scenario analyses are presented in Table 2. The EAG notes that for these three scenarios, incidence and duration of the other AEs were not changed, and that the company removed the utility decrements associated with SSEs for both treatment groups. The company does not mention any changes in the SSEs disutilities in their ACD2 response. The company justifies the use of all-grade AE incidence for neuropathy and fatigue/asthenia instead of grade ≥2 based on the absence of reported AE incidence separately for grade 2 AEs in the CARD and VISION trials, and for disutility estimates for grades 1–2.

Table 2: AE incidence rates explored in analyses

Treatment group	**^{177}Lu vipivotide tetraxetan**			**Cabazitaxel**		
Analysis/AE	**Asthenia**	**Fatigue**	**Neuropathy**	**Asthenia**	**Fatigue**	**Neuropathy**
Company's original approach (CS) to EAG preferred analyses at the ACD1 response (when included)	1.1%	5.9%	[redacted]	4.0%	0.0%	3.2%
Company's updated base case (ACD2 response)	7.0%		[redacted]	4.0%		3.2%
Company's scenario 5 (ACD2 response)	7.0%		[redacted]	4.0%		3.2%
Company's scenario 6 (ACD2 response)	49.5%		[redacted]	53.2%		19.8%
Company's scenario 7 (ACD2 response)	49.5%		[redacted]	53.2%		19.8%

Abbreviations: ACD: Appraisal Consultation Document; CS: company's submission.

The utility values applied by the company and EAG in all base case and preferred analyses during the appraisal process from the company's submission (CS) until ACD1 responses are presented in Table 3. The utility values applied by the company in the updated base case and scenario analyses in their ACD2 response and in the EAG ACD2 preferred analysis are presented in Table 4.

Table 3: Health state utility values used in scenario analysis – from CS to ACD1

	Company's original approach (CS)			EAG-preferred approach (EAG report and EAG TE and ACD1 response)			Company's updated approach (TE response)			EAG's exploratory analysis (TE-EA3)			Company's updated base case (ACD1 response)		
	177Lu	SOC	Cabazitaxel	177Lu	SOC	Cabazitaxel	177Lu	SOC	Cabazitaxel	177Lu	SOC	Cabazitaxel	177Lu	SOC	Cabazitaxel
Pre-progression	[redacted]														
Post-progression	[redacted]														
QALY losses due to AE (one-off)	-	-	-	[redacted]			-	-	-	-	-	-	-	-	-
QALY losses due to SSEs (one-off at the point of progression)	-	-	-	[redacted]			-	-	-	-	-	-	-	-	-
AE duration (months)	1.0			1.0			1.0			1.0			1.0		

Abbreviations: 177Lu: Lutetium-177 vipivotide tetraxetan; ACD1: Appraisal Consultation Document 1; AE: adverse events; CS: company submission; EAG: External Assessment Group; QALY: quality-adjusted life year; SOC: standard of care; SSE: symptomatic skeletal event; TE: technical engagement.

Table 4: Health state utility values used in company's updated base case and scenario analysis presented in ACD2 response

	Company's updated base case and EAG scenarios 4 to 6 (ACD2 response)			Company's scenario 5 (ACD2 response)		Company's scenario 6 (ACD2 response)		Company's scenario 7 (ACD2 response)		EAG-preferred approach (ACD2 response, EAG scenarios 1 to 3)		
	177Lu	SOC	Cabazitaxel	177Lu	Cabazitaxel	177Lu	Cabazitaxel	177Lu	Cabazitaxel	177Lu	SOC	Cabazitaxel
Pre-progression	[redacted]											
Post-progression												
QALY losses due to AE (one-off)	-	-	-	[redacted]	-0.0125	[redacted]						
QALY losses due to SSEs (one-off at the point of progression)	-	-	-	0.0	0.0	0.0	0.0	0.0	0.0	[redacted]		
AE duration (months)	1.0			1.0		1.0	1.0/ 5.06*	1.0	1.0/ 5.06*	1.0		1.0/ 5.06*

Abbreviations: 177Lu: Lutetium-177 vipivotide tetraxetan; ACD2 - Appraisal consultation document 2; AE: adverse events; EAG: External Assessment Group; QALY: quality-adjusted life year; SOC: standard of care; SSE: symptomatic skeletal event.

**The AE duration was assumed 5.06 months only for the neuropathy and fatigue/asthenia AEs, the remaining AEs were assumed to last 1.0 month.*

EAG critique: Overall, the EAG's view remains unchanged from that presented in the original EAG report, TE response and ACD1 response. The EAG considers that, although the treatment-independent utility estimates may not consider the full impact of receiving further chemotherapy on patients' health-related quality of life (HRQoL), the company has not provided any further evidence on the extent and duration of the additional burden associated with treatment with cabazitaxel.

The EAG also considers that including the all-grade incidence for neuropathy and fatigue/asthenia does not adequately reflect the Committee's preferences and is likely to overestimate the impact on cabazitaxel, since it includes patients with mild (grade 1) AE events. The company assumes, in the absence of separate data for grade ≥2 AEs, that patients with mild fatigue/asthenia or neuropathy, which might not require any interventions, would incur the same disutility and costs than patients with moderate, severe or potentially life-threatening AEs. It is unclear what proportion of the additional patients in the CARD and VISION trials included in the company's new scenarios had moderate (grade 2) AEs that would require treatment or would impact on the patients' overall HRQoL.

Nonetheless, based on previous feedback received from clinical and patients' experts in the Appraisal Committee meetings, the EAG agrees that the duration of some AEs might be longer for patients receiving cabazitaxel. Therefore, in the absence of data for grade 2 AEs, the EAG agrees with the inclusion of the additional AE duration for these selected events (5.06 months) for cabazitaxel patients as being more consistent with the Committee's preferences. However, the EAG cautions that without clinical evidence on this issue it is difficult to estimate if it adequately reflects the additional burden associated with patients receiving cabazitaxel post-docetaxel.

The EAG included, as part of the analyses presented in Section 4, the treatment-independent utilities approach as part of the EAG's scenario analyses 1 to 3, which includes: (i) the same utility values from the company's original analyses for the pre and post-progression health states; (ii) only grade ⩾3 AEs for all events; (iii) the assumption that neuropathy and fatigue/asthenia AEs last for the whole duration of treatment for patients receiving cabazitaxel (5.06 months). The EAG's scenarios 1 to 3 also include utility decrements associated with SSEs for both treatment groups. In line with the Appraisal Committee's suggestion that "*scenarios including treatment-dependent and treatment-independent utility values would be helpful",* the EAG also presents a separate additional set of analyses where the treatment-dependent utilities are used, in line with the company's updated base case analysis presented as part of their response to ACD2.

2.6 Issue 6: The PSMA testing costs

In response to the NICE ACD2 document,[2] the company updated its base case analysis to include the cost of PSMA testing where 62.5% of patients in the ^{177}Lu vipivotide tetraxetan treatment group were assumed to receive PSMA tests, based on the Committee's preferences and feedback from clinical experts in the ACD2, where they stated that "*The clinical lead for the Cancer Drugs Fund noted that routine access to PSMA testing can depend on geographical location. They also noted that accounting for the costs of PSMA testing in 50% to 75% of the patient population [with hormone-relapsed metastatic prostate cancer] is appropriate.*"

In the updated model, the company included costs related to receiving either a PET-CT or SPECT scan as part of PSMA testing for 62.5% of patients receiving ^{177}Lu vipivotide tetraxetan, in line the Appraisal Committee's preference. The company has also presented scenario analyses where the proportion of patients receiving the test is varied to 50% and 75% (company's ACD2 response scenarios 8 and 9, respectively), and notes that this had a limited impact on the cost-effectiveness estimates.

EAG critique: The EAG agrees with the inclusion of the analyses presented by the company for PSMA testing costs. The company has included the costs of PET-CT and SPECT-CT based on a weighted mean cost using data from the NHS Reference Costs, in line with previous scenario presented by the EAG. Therefore, the EAG has no further comments on this issue.

3 Company's updated economic analyses

The company has submitted an updated version of the economic model as part of their ACD2 response, which includes most of the Appraisal Committee preferred analysis and assumptions. The EAG adopted a number of approaches to explore and check the company's updated version of the model. The EAG believes the company's model to be generally well programmed. Nonetheless, the EAG notes that during the verification of the new version of the submitted model, the EAG has identified that one additional amendment in relation to the EAG's preferred analyses at ACD1 have been disregarded by the company, and are not mentioned by the company in the ACD2 response, which relates to the exclusion of the SSEs disutilities when using the treatment-independent approach for utilities.

The results of the company's revised base case analysis and additional scenario analyses are summarised in Table 5. The company's revised deterministic base case incremental cost-effectiveness ratio (ICER) for the comparison between ^{177}Lu vipivotide tetraxetan and cabazitaxel is £38,567 per quality-adjusted life year (QALY) gained. The revised deterministic base case ICER against SOC is £ 123,016. The EAG notes that company presented only deterministic results for their updated model at their ACD2 response.

Table 5: Results of company's revised base case and scenario analyses presented in ACD2 response (pairwise comparison against cabazitaxel, deterministic)

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. Costs	ICER
Company's revised base case model following ACD2 (deterministic)							
177Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,567
Cabazitaxel	[redacted]	[redacted]	[redacted]				
Scenario 1: Alternative OS HR from MAIC (before weighting)							
177Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,260
Cabazitaxel	[redacted]	[redacted]	[redacted]				
Scenario 2: Alternative OS and rPFS HRs from MAIC (after weighting)							
177Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,523
Cabazitaxel	[redacted]	[redacted]	[redacted]				
Scenario 3: Alternative OS and rPFS HRs from MAIC (before weighting)							
177Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,388
Cabazitaxel	[redacted]	[redacted]	[redacted]				
Scenario 4: Alternative OS HR from EAG's NMA							
177Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£369,593
Cabazitaxel	[redacted]	[redacted]	[redacted]				
Scenario 5: Treatment-independent utilities, only grade ≥3 but extended disutility duration for neuropathy and fatigue for cabazitaxel							
177Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,934
Cabazitaxel	[redacted]	[redacted]	[redacted]				
Scenario 6: Treatment-independent utilities, grade ≥1 for neuropathy and fatigue for both groups but normal disutility duration for these AEs for cabazitaxel							
177Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,206
Cabazitaxel	[redacted]	[redacted]	[redacted]				
Scenario 7: Treatment-independent utilities, grade ≥1 for neuropathy and fatigue for both groups and extended disutility duration for these AEs for cabazitaxel							
177Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,896
Cabazitaxel	[redacted]	[redacted]	[redacted]				
Scenario 8: PSMA testing included for 50% of patients receiving 177Lu							
177Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,202
Cabazitaxel	[redacted]	[redacted]	[redacted]				
Scenario 9: PSMA testing included for 75% of patients receiving 177Lu							
177Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,931
Cabazitaxel	[redacted]	[redacted]	[redacted]				

Abbreviations: 177Lu: Lutetium-177 vipivotide tetraxetan; LYG: life year gained; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; NMA: network meta-analysis; OS: overall survival; rPFS: radiographic progression-free survival; PSMA: prostate-specific membrane antigen.

Table 6: Results of company's revised base case and scenario analyses presented in ACD2 response (pairwise comparison against SOC, deterministic)

Option	LYGs*	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. Costs	ICER
Company's revised base case model following ACD2 (deterministic)*							
177Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£123,016
SOC	[redacted]	[redacted]	[redacted]				
Scenario 1: Decreased OS and rPFS hazards for 177Lu and SOC based on Ahmadzadehfar et al. (2021) univariate analysis (weighted HR = 0.649)							
177Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£86,008
SOC*	[redacted]	[redacted]	[redacted]				
Scenario 2: Decreased OS and rPFS hazards for 177Lu and SOC based on Ahmadzadehfar et al. (2021) multivariate analysis (weighted HR = 0.673)							
177Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£88,621
SOC*	[redacted]	[redacted]	[redacted]				

Abbreviations: 177Lu: Lutetium-177 vipivotide tetraxetan; SOC: standard of care; LYG: life year gained; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; SA - scenario analysis; ACD; NMA: network meta-analysis; OS: overall survival; rPFS: radiographic progression-free survival; PSMA: prostate-specific membrane antigen.
*The only change related to these analyses in comparison to the analysis presented at ACD1 relates to the cost of PSMA test.

4 Additional analyses undertaken by the EAG

This section presents the additional analyses undertaken by the EAG in order to explore the areas of uncertainty discussed in Section 2. The EAG performed six exploratory analyses. All analyses include the Committee's preferred assumption for the costs of PSMA test (for 62.5% of patients in the ^{177}Lu vipivotide tetraxetan treatment group, as included in the company's response to ACD2 base case) and using the RWE data for cabazitaxel as the baseline to estimate OS and rPFS for ^{177}Lu vipivotide tetraxetan.

The EAG's scenarios 1 to 3 include exploring three different approaches for estimating the relative effect of cabazitaxel:

(1) using the EAG NMA estimates for rPFS and OS (updated NMA presented at the ACD1 stage which includes only the direct evidence to inform the relative effect of cabazitaxel and ARPI (the CARD trial), uses a random effects model with an informative prior to inform the estimation of the between-study heterogeneity, and uses the IPCW-adjusted VISION data for OS and the interval imputed VISION data for rPFS; similar to the approach presented in the company's scenario 4);
(2) using the estimates of relative effect of cabazitaxel from the unanchored MAIC (after weighting) for OS and rPFS (similar to the approach presented in the company's scenario 2); and
(3) using the estimates of relative effect of cabazitaxel from the Bucher ITC (not presented by the company in their response to ACD2).

The EAG's scenario analyses 1 to 3 also use the treatment-independent approach to utilities using the utility values presented in the CS, and including utility decrements for AEs and SSEs with the disutilities

for SSEs obtained from the PREVAIL study. The EAG also included only the impact of grade 3+ AEs for fatigue/asthenia and neuropathy, but incorporates the company's assumption that these two AEs would last 5.06 months for patients receiving cabazitaxel.

The EAG also undertook scenarios 4 to 6, which include the three sets of approaches for estimating the relative effect of cabazitaxel as in scenarios 1 to 3, but using treatment-dependent utility values from the original utility analysis and assuming cabazitaxel utilities are half-way between utilities for ^{177}Lu vipivotide tetraxetan and SOC as in TE-EA3 (as in per the company's revised base cases at ACD2).

The results of the EAG's additional analyses are presented as pairwise comparisons between ^{177}Lu vipivotide tetraxetan and cabazitaxel in Table 7, and between ^{177}Lu vipivotide tetraxetan and SOC in Table 8. The EAG notes that it has not included any scenarios that explore adjustments to the rPFS and OS estimates to reflect decreased hazards for patients medically unsuitable for taxanes in the comparison of ^{177}Lu vipivotide tetraxetan versus SOC (see Section 2.4 issue 4).

The company's updated base case at ACD2 leads to deterministic ICERs for ^{177}Lu vipivotide tetraxetan versus cabazitaxel of £38,567per QALY gained and versus SOC of £123,016 per QALY gained. Using the EAG preferred assumptions for utilities (i.e., treatment-independent approach) and different approaches for the treatment effect estimates for cabazitaxel versus ^{177}Lu vipivotide tetraxetan leads to ICERs for ^{177}Lu vipivotide tetraxetan versus cabazitaxel of £1,109,564 per QALY gained (EAG's scenario 1 which uses EAG's NMA), £41,847 per QALY gained (when using the company's MAIC weighted in EAG's scenario 2) and £73,602 per QALY gained when using the company's Bucher ITC (EAG's scenario 3). These ICERs are considerably higher than the company's revised base case ICER, with exception of when using the company's MAIC estimates for OS and rPFS.

The chosen approach for HR estimates for OS and rPFS still represents the key driver of the ICER results in the model. The assumption of treatment-dependent utility values and the assumption regarding the utility values for cabazitaxel still has an important impact on the ICER for the comparison against cabazitaxel, which is reduced from £1,109,564 to £369,593 per QALY gained when using HR estimates from the EAG's NMA but including treatment-dependent utility values. The chosen approach for utilities in the comparison against SOC has a lower impact on the ICER, where both scenarios present ICERs higher than £100,000 per QALY gained.

In summary, the ICER is highly uncertain for ^{177}Lu vipivotide tetraxetan versus cabazitaxel with the lowest ICER generated from the EAG's ACD2 scenario 2 (£41,847 per QALY gained) to the EAG's ACD2 scenario 1 (£1,109,564 per QALY gained) when using the EAG preferred assumptions for utilities. The EAG cautions the interpretation of the lowest ICER as the company's unanchored MAIC

estimate was used for estimating the relative treatment effect of ^{177}Lu vipivotide tetraxetan versus cabazitaxel and the unanchored MAIC approach is subject to substantial uncertainty.

Table 7: Results of additional exploratory analyses undertaken by the EAG (pairwise comparisons against cabazitaxel, deterministic)

Option	LYGs*	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. Costs	ICER
Company's revised base case model following ACD1							
177Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£47,827**
Cabazitaxel							
EAG preferred analysis at ACD1 (new NMA + PSMA costs 100% pts + cost of additional AEs included)							
177Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£1,253,078**
Cabazitaxel							
ACD1 EA1: EAG preferred at ACD1 + utility treatment-dependent (as in TE-EA3)							
177Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£318,260**
Cabazitaxel							
Company's revised base case model following ACD2							
177Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£38,567**
Cabazitaxel							
EAG ACD2 scenario 1 (EAG's NMA estimates for OS and rPFS, treatment-independent utilities*)							
177Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£1,109,564**
Cabazitaxel							
EAG ACD2 scenario 2 (company's MAIC after weighting estimates for OS and rPFS, treatment-independent utilities*)							
177Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£41,847**
Cabazitaxel							
EAG ACD2 scenario 3 (company's Bucher ITC estimates for OS and rPFS, treatment-independent utilities*)							
177Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£73,602**
Cabazitaxel							
EAG ACD2 scenario 4 (EAG's NMA estimates for OS and rPFS, treatment-dependent utilities‡)†							
177Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£369,593**
Cabazitaxel							
EAG ACD2 scenario 5 (company's MAIC after weighting estimates for OS and rPFS, treatment-dependent utilities‡)†							
177Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£38,523**
Cabazitaxel							
EAG ACD2 scenario 6 (company's Bucher ITC estimates for OS and rPFS, treatment-dependent utilities‡)							
177Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£64,245**
Cabazitaxel							

Abbreviations: 177Lu: Lutetium-177 vipivotide tetraxetan; SOC: standard of care; LYG: life year gained; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio.

*The approach using treatment-independent utilities also include disutilities associated with SSEs and grade ≥3 AEs, and 5.06 months duration for cabazitaxel fatigue/asthenia and neuropathy AEs

‡Treatment-dependent utility values using the same assumptions as in EAG's TE-EA3.

†The EAG's scenarios 4 (using treatment-dependent utilities and EAG's NMA estimates) and 5 (using treatment-dependent utilities and MAIC weighted estimates for OS and rPFS and treatment-dependent utilities) *correspond to the company's ACD2 scenarios 4 and 2, respectively.*

Table 8: Results of additional exploratory analyses undertaken by the EAG (pairwise comparisons against SOC, deterministic)

Option	LYGs*	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. Costs	ICER
Company's revised base case model following ACD1							
177Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£117,360**
SOC	[redacted]	[redacted]	[redacted]				
EAG preferred analysis at ACD1 (new NMA + PSMA costs 100% pts + cost of additional AEs included)							
177Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£150,511**
SOC	[redacted]	[redacted]	[redacted]				
ACD1 EA1: EAG preferred at ACD + utility-dependent (as in TE-EA3)							
177Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£124,162**
SOC	[redacted]	[redacted]	[redacted]				
Company's revised base case model following ACD2							
177Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£123,016**
SOC	[redacted]	[redacted]	[redacted]				
EAG ACD2 scenarios 1 to 3 (treatment-independent utilities*)†							
177Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£148,663**
SOC	[redacted]	[redacted]	[redacted]				
EAG ACD2 scenarios 4 to 6 (treatment-dependent utilities‡)†							
177Lu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£123,016**
SOC	[redacted]	[redacted]	[redacted]				

Abbreviations: 177Lu: Lutetium-177 vipivotide tetraxetan; SOC: standard of care; LYG: life year gained; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio.

*The approach using treatment-independent utilities also include disutilities associated with SSEs and grade ≥3 AEs, and 5.06 months duration for cabazitaxel fatigue/asthenia and neuropathy AEs

‡Treatment-dependent utility values using the same assumptions as in EAG's TE-EA3.

†EAG ACD2 scenarios 1 to 3 and 4 to 6 do not differ within them in the comparison against SOC, since the main difference between them is the approach to the treatment effect between ^{177}Lu vipivotide tetraxetan and cabazitaxel included, so no applicable to the comparison against SOC.

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